Clinical Trial Protocol

Protocol Title:

A Prospective Phase 1b/2a, Active-controlled, Randomized, Open-label Study to Evaluate the Safety, Tolerability, Extended Early Bactericidal Activity and Pharmacokinetics of Multiple Oral Doses of BTZ-043 Tablets in Subjects With Newly Diagnosed, Uncomplicated, Smear-positive, Drug-susceptible Pulmonary Tuberculosis

Protocol Number:

PanACEA – BTZ-043 - 02

Protocol Version

V5.0

Protocol Date

May 5th, 2021

Sponsor

Sponsor	LMU Klinikum Marchioninistr. 15 D-81377 Munich Phone : 089 4400 - 0 Email: info@klinikum.uni-muenchen.de
Sponsor Delegated Person	**Prof. Dr. med. Michael Hoelscher** Division of Infectious Diseases and Tropical Medicine LMU Klinikum Leopoldstrasse 5 D-80802 München / Germany Phone: +49 89 4400 598 00 Email: hoelscher@lrz.uni-muenchen.de
Sponsor Medical Experts / Immediately Reportable Events	**Dr. Leoni Matt** Division of Infectious Diseases and Tropical Medicine LMU Klinikum Leopoldstrasse 5 D-80802 München / Germany Phone: +49 89 4400 598-47 Email: matt@lrz.uni-muenchen.de **Dr. Norbert Heinrich** Division of Infectious Diseases and Tropical Medicine LMU Klinikum Leopoldstrasse 5 D-80802 München / Germany Phone: +49 89 4400 598 05 Email: heinrich@lrz.uni-muenchen.de
Study Statistician	**Dr. Patrick Phillips** University of California, San Francisco Department of Medicine, Division of Pulmonary & Critical Care Medicine 1001 Potrero Avenue San Francisco, CA 94110 United States Phone: +1 415.206.3960 Email: Patrick.Phillips@ucsf.edu
Pharmacological Expert:	**Dr. Rob Aarnoutse** Radboud University Nijmegen Medical Centre Department of Pharmacy Geert Grooteplein 10, P.O. Box 9101

	6500 HB Nijmegen /The Netherlands Phone: + 31 24 361 6405 Email: Rob.Aarnoutse@radboudumc.nl
Sponsor Monitor	**Dr. Julia Dreisbach** Division of Infectious Diseases and Tropical Medicine LMU Klinikum D-80802 München / Germany Phone: +49 89 4400 598 25 Email: dreisbach@lrz.uni-muenchen.de **Dr. Petra Gross-Demel** Division of Infectious Diseases and Tropical Medicine LMU Klinikum D-80802 München / Germany Phone: +49 152 26309142 Email: Gross-Demel@lrz.uni-muenchen.de
CRO Project Manager	**Melene Strauss** TCD Global Design House, 121 Amkor Road, Centurion, 0157, South Africa PO Box 15775, Lyttelton, 0140, South Africa Phone: +27 12 664 1622 Email: Melene.Strauss@tcd-global.com
South African Study Centres	**TASK Applied Science Clinical Research Centre** **Site PI: Dr Veronique de Jager** 1 Small Street Boston, Belville 7530 Cape Town South Africa Phone: +27 21 917 1044/45 Email: dr.veronique@task.org.za **University of Cape Town Lung Institute (UCTLI)** **Site PI: Dr. Rodney Dawson** George Street Mowbray 7700 Cape Town South Africa Phone: +27 21 406 6850 / +27 21 650 1910 Email: rodney.dawson@uct.ac.za
Country PI South Africa	**Prof. Dr. Andreas Diacon** TASK Applied Science Clinical Research Centre 1 Small Street Boston, Belville 7530 Cape Town

	South Africa Phone: +27 21 917 1044/45 Email: ahd@sun.ac.za

Signature Page

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Protocol Number:	PanACEA – BTZ-043 – 02
Protocol Version:	V5.0, dated May 5th, 2021

Sponsor

Herewith we approve the protocol PanACEA – BTZ-043 – 02, V5.0, dated May 5th, 2021, and confirm that it contains all information necessary to conduct the trial according to Good Clinical Practice, all applicable local regulations and the ethical principles laid down in the Declaration of Helsinki.

Sponsor Delegated Person
Prof. Dr. med. Michael Hoelscher
Division of Infectious Diseases and Tropical Medicine
LMU Klinikum

05.05.21
Date

Principal Investigator Signature Page

Herewith I confirm that I have read and understood the protocol PanACEA – BTZ-043 – 02, V5.0, dated May 5th, 2021, and agree to conduct this clinical trial accordingly, including all statements regarding compliance with Good Clinical Practice, all applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki.
I will provide copies of the protocol and all information to the site personnel under my supervision required to conduct the clinical trial duly. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Veronique de Jager
Principal Investigator Name

Principal Investigator Signature

Cape Town, 06 May 2021.
Place and Date

Principal Investigator Signature Page

Herewith I confirm that I have read and understood the protocol PanACEA – BTZ-043 – 02, V5.0, dated May 5th, 2021, and agree to conduct this clinical trial accordingly, including all statements regarding compliance with Good Clinical Practice, all applicable local regulations, and the ethical principles laid down in the Declaration of Helsinki.

I will provide copies of the protocol and all information to the site personnel under my supervision required to conduct the clinical trial duly. I will discuss this material with them and ensure they are fully informed on all trial requirements.

Professor Rodney Dawson

Principal Investigator Name

Digitally signed by Rod Dawson
Date: 2021.05.06 '10:33:08 +02'00

Principal Investigator Signature

Cape Town, South Africa

Place and Date

7 DEC 2021

Synopsis

Protocol Title	A Prospective Phase Ib/IIa, Active-controlled, Randomized, Open-label Study to Evaluate the Safety, Tolerability, Extended Early Bactericidal Activity and Pharmacokinetics of Multiple Oral Doses of BTZ-043 Tablets in Subjects With Newly Diagnosed, Uncomplicated, Smear-positive, Drug-susceptible Pulmonary Tuberculosis
Protocol Code	PanACEA-BTZ-043-02
Short Title	BTZ-043 Phase Ib/IIa Study
Sponsor	LMU Klinikum Marchioninistr. 15 D-81377 München / Germany
Study Centres	This will be a multi-centre study in two sites in Cape Town/South Africa.
Name of Investigational Medicinal Product (IMP)	**BTZ-043**
Non-IMP study drugs	**Rifafour e-275®** (or equivalent) Each tablet Rifafour e-275® contains Isoniazid, Rifampicin, Pyrazinamide and Ethambutol as: • Rifampicin 150 mg • Isoniazid 75 mg • Pyrazinamide 400 mg • Ethambutol 275 mg **Probe Drug Cocktail, containing:** • Caffeine: 1 tablet à 150mg • Tolbutamide: 1/4 tablet à 500mg (≡ 125 mg) • Dextromethorphan: 10mL syrup à 15mg/5mL (≡ 30 mg) • Digoxin: 2 tablets à 0.25mg (≡ 0.5mg) • Midazolam: 2mL i.v.solution à 5mg/5mL p.o. (≡ 2mg) **Dolutegravir:** 1 tablet à 50mg
Indication	Uncomplicated, Newly Diagnosed, Drug Sensitive Pulmonary Tuberculosis
Objectives	Primary Objective: To assess the safety and tolerability of BTZ-043 given once or twice daily over 14 days by evaluation of Adverse Events (AEs) during treatment and follow-up period in patients with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary tuberculosis Secondary Objectives: 1. *Secondary bactericidal activity objectives:*

	To evaluate the bactericidal activity of different doses of BTZ-043, given once or twice daily over 14 days, by investigating the change in viable mycobacterial load in liquid and on solid culture, lipoarabinomannan (LAM) load and mycobacterial ribonucleic acid (RNA) (molecular bacterial load assay, MBLA) in sputum over time between day -1 and day 15. 2. <u>*Secondary pharmacokinetic objectives:*</u> a) To describe the pharmacokinetics (PK) of BTZ-043, and its major metabolites, after a single or split-dose, and at steady state b) To analyse the population PK of BTZ-043 and its main metabolites to quantify inter-individual variability, suitable for evaluation of alternative dosing regimens c) To determine the effect of a high-fat high-calorie meal on exposure by evaluating the PK of BTZ-043 within 24 hours after fasting intake of BTZ-043 vs. intake after a defined high-caloric meal at steady state (stage 1) *d)* To assess the effect of BTZ-043 on the activity of hepatic cytochrome P (CYP) 450 enzymes, P-glycoprotein, and the metabolism of dolutegravir, as measured by accelerated versus inhibited metabolism of either a pre-defined probe drug cocktail or of dolutegravir (stage 2) *e)* To complement drug–drug interaction risk assessment via investigation of appropriate endogenous biomarker(s)
Study Design	This is a prospective, open label, two-centre, randomized, controlled, two-stage, phase Ib/IIa study to evaluate the safety, tolerability, PK, drug-drug interaction and bactericidal activity of BTZ-043 administered orally once or twice daily over 14 days to participants with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary tuberculosis: **Stage 1:** – Focusing on adverse events, PK and a food-effect PK evaluation in an escalating dose design in up to eight cohorts receiving different doses of BTZ-043 to define a safe dose corridor for BTZ-043 **Stage 2:** – Focusing on adverse effects, early bactericidal activity (EBA), PK and an evaluation of PK drug-drug interaction potential through prospective randomization to four arms: three arms to receive BTZ-043 in different doses within the safe corridor defined in stage 1, compared to one arm receiving Rifafour e-275®control. An interim analysis will be done after 5 patients per BTZ-043 receiving arm 1-3 complete treatment. The TSC will review the results of this analysis and consider whether to include up to two additional arms of BTZ-043. At least one of these

	additional BTZ-043 arms may be a split-dose arm. These arms (arm 5 and arm 6) will be dosed in the dose range proven safe in stage 1. After the course of study drugs is completed (on day 14), patients will be referred to a government clinic to complete their tuberculosis (TB) treatment, according to national governmental standards for a total of 6 months of first-line therapy. Allocation of up to 77patients (105 if two additional arms are added) will be carried out in two stages: • 1st stage: for each cohort 3 patients will be enrolled, treated and followed-up accordingly, starting with cohort 1. In a Trial Steering Committee (TSC) meeting, decision will be made on the dose in the next cohort. • 2nd stage: after the highest possible dose of the investigational drug, that has proven to be safe within the 1st stage, is identified, all remaining patients will be recruited and randomised to receive one of three different doses of BTZ-043 or to control treatment with Rifafour e-275® (or equivalent) at a ratio of 3:3:3:2 favouring the experimental treatment. For allocation to 5th and 6th arms, see p. 69. <u>1st stage - Dose escalation steps to be followed if no safety concerns arise:</u> • Cohort 1: patients to receive 250 mg BTZ-043 • Cohort 2: patients to receive 500 mg BTZ-043 • Cohort 3: patients to receive 750 mg BTZ-043 • Cohort 4: patients to receive 1000 mg BTZ-043 • Cohort 5: patients to receive 1250 mg BTZ-043 • Cohort 6: patients to receive 1500 mg BTZ-043 • Cohort 7: patients to receive 1750 mg BTZ-043 • Cohort 8: patients to receive 2000 mg BTZ-043 Patients receiving the investigational drug in cohorts 1 – 8 during the first stage will take BTZ-043 in fasting state for 13 days and after a pre-defined high-fat, high-caloric meal on day 14. After all patients of a current cohort have completed a dosing of at least 7 days of dosing, or earlier in exceptional cases, the TSC, composed of the national principal investigator (PI), the trial statistician and the sponsor representative, and three independent experts will review safety data, including clinical, lab and electrocardiography (ECG) data, to assess whether dose limiting toxicity of BTZ-043, as defined below, has been observed in any participant. Depending on the outcome, the TSC will then decide on dose escalation, or on enrolling more participants to the same

	or a lower dose in the following cohort, according to dose escalation and stopping rules. Stage 1 was completed with 24 patients allocated to 7 cohorts. The 8th cohort was not conducted. After the end of stage 1, the TSC decided which of the BTZ-043 doses, which are deemed to not exceed the acceptable toxicity level, are to be moved to stage 2. All remaining participants will be randomized prospectively to one of the following arms: 2nd stage - Allocation of patients: • Arm 1: approx. 14 patients to receive BTZ-043 1000mg • Arm 2: approx. 14 patients to receive BTZ-043 500mg • Arm 3: approx. 14 patients to receive BTZ-043 250mg • Control Arm 4: approx. 11 patients to receive Rifafour e-275® (or equivalent).as control treatment • Arm 5 and 6: up to 14 patients (per arm) to receive BTZ-043 in a dose to be determined after review of first data of Arms 1-3, in the dose range proven safe in Stage 1. Participants will take in BTZ-043 in fed state, because intake of BTZ-043 after a meal led to higher exposure during 1st stage. Additional measurements in the 2nd stage in BTZ-arms only: • Drug-drug interactions will be investigated: patients, who have been randomized to BTZ-043 arms 1-3, will additionally be randomized to receive either a probe drug cocktail, with drugs specifically metabolized by certain enzymes, or dolutegravir at a ratio of 2:1. Probe drug cocktail or DTG will be given pre-BTZ on day 0 and on day 14. • Blood samples will be collected for the pharmacokinetic characterisation of BTZ-043 and its main metabolites. • Blood samples will be collected for the pharmacokinetic characterizations of alterations in the probe drug metabolism and to investigate the most appropriate endogenous biomarker(s) to complement drug–drug interaction risk assessment • If deemed necessary, a 24-hour urine collection to investigate the most appropriate endogenous biomarker(s) to complement drug–drug interaction risk assessment will be collected and evaluated
Population	Up to 105 male and female patients, aged ≥ 18 – 64 years, with newly diagnosed, smear positive, drug sensitive pulmonary tuberculosis will be enrolled.

	In case of a high number of dropouts or non-evaluable patients, it may be necessary to recruit more participants into the study, (see sample size considerations).
Sample Size	<u>To be analysed in the 1st Stage:</u> N = 3 patients per cohort. Additional patients may be added to a dosing cohort, if the TSC sees a requirement for a higher patient number at a given dose <u>To be analysed in the 2nd Stage:</u> All remaining participants, up to a total number (N) = 105 In case of a high number of dropouts or non-evaluable patients, more patients may be recruited.
Dosage and Administration	<u>1st Stage (Design, if the TSC does not face any safety concerns. In case the TSC rises safety concerns, the following cohort may receive an equal or lower dose):</u> • Cohort 1 (BTZ_{250}): 3 patients will receive 250 mg of BTZ-043 • Cohort 2 (BTZ_{500}): 3 patients will receive 500 mg of BTZ-043 • Cohort 3 (BTZ_{750}): 3 patients will receive 750 mg of BTZ-043 • Cohort 4 (BTZ_{1000}): 3 patients will receive 1000 mg of BTZ-043 • Cohort 5 (BTZ_{1250}): 3 patients will receive 1250 mg of BTZ-043 • Cohort 6 (BTZ_{1500}): 3 patients will receive 1500mg of BTZ-043 • Cohort 7 (BTZ_{1750}): 3 patients will receive 1750mg of BTZ-043 • Cohort 8 (BTZ_{2000}): 3 patients will receive 2000mg of BTZ-043 <u>2nd Stage:</u> After determination of the safe dose corridor in stage 1, the TSC has chosen three dose levels BTZ_{high}, BTZ_{med}, BTZ_{low} within this corridor to generate more data on safety and bactericidal activity. From a total of up to 105 patients combined in stage 1 and 2, the remaining patients for stage 2 will be prospectively randomised to receive either one of the 3 selected dose levels of the investigational product or the control regimen at a ratio of 3:3:3:2 favouring the experimental treatment. Approx. 14 patients will be randomised to each of the experimental dose arms, and approx. 11 will be randomised to control treatment: • Arm 1 (BTZ_{high}) with a higher dosage of BTZ-043, proven to be safe in 1st stage: 14 Patients will be randomized to receive 1000mg of BTZ-043 • Arm 2 (BTZ_{med}) with a medium dosage of BTZ-043, proven to be safe in 1st stage: 14 Patients will be randomized to receive 500mg of BTZ-043 • Arm 3 (BTZ_{low}) with a lower dosage of BTZ-043 proven to be safe in 1st stage: 14 Patients will be randomized to receive 250mg of BTZ-043 • Arm 4 (control): 11 patients will be randomized to receive a standard dose of Rifafour e-275® (or equivalent) according to body weight.

	• Optional BTZ-Arms (Arm 5 and Arm 6): dosage will be in the dose range proven safe in Stage 1. **BTZ-043:** Dose escalation in stage 1 will be carried out sequentially. The TSC will decide on the dose escalation for the next cohort after review of the safety data from the current cohort. Daily doses of 250mg, 500 mg, 750mg, 1000mg, 1250 mg, 1500 mg, 1750 mg or 2000mg to be given once daily to fasting patients on day 1-13 and after a pre-defined breakfast on day 14. In stage 2, for the patients to receive BTZ043, a pre-defined breakfast will be provided by the sites. For optional arms with split-dose administration, patients will be provided a pre-defined meal to be taken with the evening dose of BTZ-043. **Rifafour e-275® (or equivalent):** daily doses to be given adapted to body weight to fasting patients, in accordance with South African Guidelines for treatment of TB: • 38-54 kg: 3 tablets • 55 – 70 kg: 4 tablets • > 70 kg: 5 tablets (weight to be rounded off to the nearest integer) **Probe Drugs:** the following drugs will be given to patients in BTZ-043 arms 1-3 during stage 2, after inclusion on day 0 and on day 14, depending on second randomization: **EITHER** • **Probe Drug Cocktail (consisting of):** – Caffeine: 1 tablet à 150mg – Tolbutamide: 1/4 tablet à 500mg (≡ 125 mg; after weight control of split tablet) – Dextromethorphan: 10mL syrup à 15mg/5mL (≡ 30mg) – Midazolam: 2mL solution à 5mg/5mL orally (≡ 2mg) – Digoxin: 2 tablets à 0.25mg (≡ 0.5mg) **OR** • **Dolutegravir:** 1 tablet à 50mg
Evaluation Criteria	Patients will be regularly assessed for adverse events (AEs), including vital signs, physical examinations, weight, neurological and ophthalmological examinations, 12-lead ECG, routine clinical laboratory tests (including chemistry, haematology and urinalysis data) **Primary Endpoint:** Safety and tolerability of BTZ-043 as assessed by evaluation of AEs during treatment- and follow-up phase, including: • clinical observations • changes in vital signs • changes in serum chemistry, haematology, coagulation and urinalysis parameters with baseline measurements • changes in ECG, incl. heart rate, PR interval, QRS, QT interval, QT interval corrected for heart rate using Fridericia´s correction,

	(QTcF); change of QTcF from baseline to post-dose measurements; morphological abnormalities **Secondary Endpoints:** 1. <u>Secondary Bactericidal Activity Endpoints:</u> The bactericidal activity of different doses (and different dosing intervals in optional arms) of the BTZ-043 will be evaluated by measuring the rate of change in sputum viable bacterial load between day -1 and day 14 by a change in the following endpoints that describe bacterial load per sample: • changes in time to detection in the BD MGIT™ liquid media culture system from baseline • changes in solid media colony forming units (CFU) from baseline • changes in sputum LAM (experimental endpoint) and sputum MBLA (experimental endpoint) from baseline 2. <u>Secondary Pharmacokinetic Endpoints:</u> a) The PK of BTZ-043 and its two major metabolites BTZ-045S and M2, and other metabolites of interest, after a single dose and split-dose at steady state will be evaluated by measuring the following parameters: • area under the plasma concentration curve from dosing to the end of the dosing interval (AUC0-24) and to infinite (AUC0-inf) • observed maximum concentration (C_{max}) • time to reach C_{max} (T_{max}) • minimum observed plasma concentration 24 hours following the last dose (C_{min}) • Clearance (Cl) • Volume of distribution (Vd) • Elimination half-life ($T_{1/2}$) • Relation of efficacy measurements to pharmacokinetic indices of BTZ-043 and its metabolites (AUC, C_{max}) (pharmacodynamics) b) A population PK-analysis of BTZ-043 and its metabolites will be carried out to quantify inter-individual variability, suitable for evaluation of alternative dosing regimens c) The effect of food on the exposure of the BTZ-043 and its metabolites will be determined by evaluating the change in PK after a high fat high calorie meal in comparison to the PK under fasting conditions during the 1st stage. d) The effect on BTZ-043 at steady state on hepatic enzyme and P-glycoprotein activity (induction vs. inhibition) will be evaluated by measuring changes in PK of the probe drugs administered on day 0, and day 14 during the 2nd stage. e) Appropriate endogenous biomarker(s) to complement drug–drug interaction risk assessment may be evaluated.
Study Timeline	Estimated date of first participant enrolled: Quarter 03/2019 Estimated date of last participant enrolled: Quarter 03/2021 Estimated date of last participant completed: Quarter 03/2021 <u>Total duration of study:</u>

	23 months (10 months enrolment period + 3 weeks treatment and post-treatment follow-up in the 1st Stage and 10 months recruitment + 3 weeks of treatment and post-treatment follow-up in 2nd Stage) <u>Study duration per participant:</u> 3 weeks (14 days treatment period + 7 days (±2 days) follow-up period.
Statistical Methods	The bactericidal activity of the IMP against MTB will be determined as the change in logCFU (solid media), or the change in days to positivity on MGIT over time (liquid media). This is a descriptive study with no inferential statistics or hypothesis testing. Data from patients on the control group will be included in the analysis and reported to confirm acceptable methodology and conditions for susceptibility testing. The standard EBA is the rate of change over the first two days, but it has been demonstrated for many TB drugs that the rate of change in bacterial load varies over time, and bactericidal activity may become evident only some days into the trial depending on the drug's pharmacokinetic properties. The decline in logCFU may therefore be linear, piece-wise linear (sometimes described as 'bilinear') or non-linear over each of the three time periods. Various methods will be used to explore different shapes of the decline in logCFU. These include linear and restricted cubic splines in mixed effects models to explore non-linearity, linear mixed effects models for linear models and non-linear mixed effects parametric models (such as the biexponential model) as appropriate. Due to the small number of patients, it may not be possible to fit non-linear mixed effects models to the data. The estimated slope or slopes from the selected model will be summarized for each dose group.
Safety Measures	**<u>Stopping criteria for individual patient dosing of IMP during 1st stage:</u>** <u>Blood pressure Stopping Criteria:</u> • A medium systolic blood pressure >180 mm Hg or <80 mm Hg, and/or a medium diastolic blood pressure >110 mm Hg as measured by triplicate measurements • A medium systolic blood pressure >160 mm Hg or <85 mm Hg for more than 12 hours, and/or a medium diastolic blood pressure >100 mm Hg for more than 12 hours as measured by triplicate measurements with control measurements after 4, 8 and 12 hours (in this case, study drugs will be discontinued for 24 hours and the patient's blood pressure regularly re-assessed before a decision on continuation of study drugs is made) <u>ECG Stopping Criteria</u>: A patient that meets either bulleted criterion below will be withdrawn from the study. Withdrawal of patients is to be based on an average QTcF value of triplicate ECGs during treatment phase. • QTcF >500 msec,

	• Change from baseline: increase in QTcF >60 msec Hepatotoxicity stopping criteria: • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN and/or alkaline phosphatase (ALP) >5×ULN for >7 days. • ALT or AST >8× ULN and/or alkaline phosphatase (ALP) >8× ULN • ALT or AST >3x ULN and (total bilirubin (TBL) >2xULN or INR >1.5 Other: Severe signs or symptoms, or significant changes in any of the safety assessments that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests etc.), in consultation with the sponsor medical expert. **Cohort stopping rule during 1st stage:** If ≥ 1 participants experience an SAE (not including prolongation of hospitalisation) at least possibly related to BTZ-043, all patients receiving this or higher doses of IMP will stop treatment. No dose escalation will be performed. **General stopping rules during 2nd stage:** Ad hoc TSC meeting in stage 2: if > 1 participant meets 'individual patient stopping criteria for discontinuation of IMP'
Dose escalation criteria (Stage 1)	The TSC will meet after a dosing cohort has accumulated safety data from at least 7 days of dosing or earlier, in exceptional cases. The TSC will review all available data (including data from previous cohorts) on adverse events, vital signs, laboratory and ECG results, and may decide as follows: • Increase BTZ-043 to next planned dosing level • Enrol more patients into current dose level • Enrol more patients into any lower dose level • Terminate enrolment • Terminate dosing in all active patients **Definition of dose limiting toxicities:** For hepatotoxicity, ECG and blood pressure, dose limiting toxicities are defined as under individual patient stopping criteria. For all other toxicities, the following applies: • moderate (grade 2) or higher grade toxicity (according to the Common Terminology Criteria for Adverse Events (CTCAE) V5.0, that Is at least probably related to IMP • grade 3 or higher AEs that are at least possibly related to IMP

Schedule of Events

Stage 1	Screening	Inclusion	Treatment														Discharge	Follow-up [M]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visiting Time	Day -8 to -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 22 (±3)
Informed Consent	X																	
Medical History	X																	
Demographics	X																	
Complete Physical Examination [A]	X															X		
Ophthalmological Assessment [O]	X																X	(X)
Symptom related Physical Examination [A]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital signs [B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test [C]	X															X		
Urine Drug Screening [D]	X																	
Serology (HIV, HCAb, HBsAg)	X																	
Spot sputum collection [E]	X																	
Chest X-ray [F]	X																	
Overnight sputum collection [G]	X	X		X	X	X		X		X			X			X		

Stage 1	Screening	Inclusion	Treatment														Dis-charge	Follow-up [M]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visiting Time	Day -8 to -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 22 (±3)
12-lead-ECG [H]	X[H]		X[H]						X[H]							X[H]		
Screening + Safety lab [I]	X[J]			X[J]		X			X[J]			X				X[J]		
Hospitalization	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
High-caloric breakfast																X		
Study drug administration			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Intensive PK sampling [K]			X											X		X		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Assessment (AEs/SAEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genetic testing sample[L]	X																	

A: Physical examination: (to be done within 2 hours before or after dosing): complete examination including height (visit 1 only), weight, neurological examination, incl. cranial nerves, biceps, patellar, achilles tendon reflex, equilibrium, gait, cognition (time and localisation). Symptom directed physical examination on days without complete physical examination.

B: Vital Signs: Blood Pressure and Heart Rate to be recorded after at least 10 minutes supine rest. During experimental treatment, within 2 hours before dosing and at 1h (± 15 min), 2h (± 15 min), and 8h (± 15 min) post drug-administration. Body temperature to be recorded once per visit.

C: Serum Pregnancy Test: female patients of child – bearing potential only

D: Urine Drug Screening: testing for opiates, amphetamines, cannabis, cocaine, benzodiazepines and barbiturates.

E: Spot sputum collection: to be collected for acid-fast bacilli (smear from concentrated sample) and testing for RIF- and INH-susceptibility by rapid test; multiple spots might be collected for assessments of smears and molecular resistances, if material appears to be insufficient from one spot sputum; overnight sputum may also be used for smear and susceptibility testing (such as “GeneXpert” and/or “HAIN MTBDR plus”), if spot sputum is inadequate.

F: Chest X-ray: if no chest X-ray is available no older than 2 weeks

G: Overnight sputum collection: for amount of sputum, bacterial load (time to detection in the BD MGIT™ liquid media culture system, colony forming units (CFU) on solid media, sputum LAM, sputum MBLA; at least two overnight sputa should be performed pre-treatment.
H: ECG: during screening, a single ECG is sufficient. Triplicate ECG will be recorded within 2 hours before dosing and at 1h (± 15 min), 2h (± 15 min), and 8h (± 15 min) post drug-administration. Triplicate ECGs should be collected ≥ 1 to ≤ 5 minutes apart.
I: Screening and Safety Lab: to be collected before drug administration, incl. the following parameters: glucose, uric acid, urea, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, total, direct, and indirect (calculated) bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), creatinine, estimated glomerular filtration rate (eGFR), low density lipoprotein (LDL), full blood count and dipstick urine analysis (for glucose, protein, leucocytes, erythrocytes, protein, pH, urobilinogen; microscopy to follow up on significantly abnormal dipstick results, as per the investigator's decision)
J: Labs plus Coagulation: Prothrombin time, activated partial thromboplastin time (APTT), INR
K: PK sampling (Day 1, Day 12 and Day 14): blood samples will be taken at 0.0h (pre-dose) and post-dose at 15min, 30min, 1.0h, 1.5h, 2.0h, 3.0h, 4.0h, 6.0h, 8.0h, 10.0h, 12.0h, 24.0h (pre-dose the following day). Time window: 0h – 2h (± 5 min), 3h – 24h (± 10 min)
L: Pharmacogenomics blood sample: single blood sample for possible genetic analysis if consent is given for this on a separate form.
M: Follow-up: This visit may be performed by phone while the Covid-19 pandemic is ongoing, unless there is need to follow up on new complaints reported by the patient, abnormal blood results, clinical assessments or ongoing AE's, that need to be followed-up by physical contact.
O: Ophthalmological Assessment (Day 1 and Day 15; during follow up as required): this will be carried out by an ophthalmologist affiliated to the sites by referral. The assessment includes history of eye diseases, visual acuity and refractive errors (Snellen Chart), colour vision testing (Ishihara), examination of the pupils, ocular motility and alignment, intraocular pressure, external examination of the eye, slit-lamp examination, fundoscopic examination, optical coherence tomography (OCT). An assessment at visit 18 (Day 22±3) is optional as per recommendation by the ophthalmologist, should there be any ophthalmological AEs or findings on Day 14 or later, that need to be followed up.

Stage 2	*Screening*	*Inclusion*	*Treatment*														*Dis-charge*	*Follow-up [O]*
Visit Number	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*	*11*	*12*	*13*	*14*	*15*	*16*	*17*	*18*
Visiting Time	*Day -8 to -1*	*Day 0*	*Day 1*	*Day 2*	*Day 3*	*Day 4*	*Day 5*	*Day 6*	*Day 7*	*Day 8*	*Day 9*	*Day 10*	*Day 11*	*Day 12*	*Day 13*	*Day 14*	*Day 15*	*Day 22 (±3)*
Informed Consent	X																	
Medical History	X																	
Demographics	X																	
Complete Physical Examination [A]	X															X		
Ophthalmological Assessment [P]	X														(X)	(X)	X	(X)
Symptom related Physical Examination [A]			X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital signs [B]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Pregnancy Test [C]	X															X		
Urine Drug Screening [D]	X																	
Serology (HIV, HCAb, HBsAg)	X																	
Spot sputum collection [E]	X																	
Chest X-ray [F]	X																	
Overnight sputum collection [G]	X	X		X	X	X		X		X			X			X		
12-lead-ECG [H]	X [H]		X [H]						X [H]							X [H]		
Screening + Safety lab [I]	X [J]			X [J]		X			X [J]			X				X [J]		

Stage 2	Screening	Inclusion	Treatment														Discharge	Follow-up [O]
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Visiting Time	Day -8 to -1	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 22 (±3)
Randomization [Q]	X	X																
Hospitalization	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PK probe drug administration [K]	(x)	X														X		
Study drug administration			X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Intensive PK sampling		X^{M}	X^{L}													$X^{L,M}$		
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Safety Assessment (AEs/SAEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Genetic testing sample [N]	X																	
24h urine collection [R]		X														X		

A: Physical examination: (to be done within 2 hours before or after dosing): complete examination including height (visit 1 only), weight, neurological examination, incl. cranial nerves, biceps, patellar, Achilles tendon reflex, equilibrium, gait, cognition (time and localisation). Symptom directed physical examination on days without complete physical examination.

B: Vital Signs: Blood Pressure and Heart Rate to be recorded after at least 10 minutes supine rest. During experimental treatment, within 2 hours before IMP- dosing and at 1h (± 15 min), 2h (± 15 min), and 8h (± 15 min) post IMP-drug-administration. Body temperature to be recorded once per visit.

C: Serum Pregnancy Test: female patients of child – bearing potential only

D: Urine Drug Screening: testing for opiates, amphetamines, cannabis, cocaine, benzodiazepines and barbiturates.

E: Spot sputum collection: to be collected for acid-fast bacilli (smear from concentrated sample) and testing for RIF- and INH-susceptibility by rapid test; multiple spots might be collected for assessments of smears and molecular resistances. Spot sputum **or** overnight sputum may be used for smear and susceptibility testing (such as “GeneXpert” and/or “HAIN MTBDR plus”).

F: Chest X-ray: if no chest X-ray is available no older than 2 weeks

G Overnight sputum collection: for amount of sputum, bacterial load (time to detection in the BD MGIT™ liquid media culture system, colony forming units (CFU) on solid media, sputum LAM, sputum MBLA; at least two overnight sputa should be performed pre-treatment.
H: ECG: during screening, a single ECG is sufficient. Triplicate ECG will be recorded within 2 hours before IMP dosing and at 1h (± 15 min), 2h (± 15 min), and 8h (± 15 min) post IMP drug-administration. Triplicate ECGs should be collected ≥ 1 to ≤ 5 minutes apart.
I: Screening and Safety Lab: to be collected before drug administration, incl. the following parameters: glucose, uric acid, urea, sodium, potassium, chloride, calcium, inorganic phosphorus, total protein, total, direct, and indirect (calculated) bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, gamma-glutamyl transferase (GGT), creatinine, estimated glomerular filtration rate (eGFR), low density lipoprotein (LDL), full blood count and dipstick urine analysis (for glucose, protein, leucocytes, erythrocytes, protein, pH, urobilinogen; microscopy to follow up on significantly abnormal dipstick results, as per the investigator's decision)
J: Labs plus Coagulation: Prothrombin time, activated partial thromboplastin time (APTT), INR
K: PK probe drug administration: patients **in BTZ- 043 Arms 1-3 only** will be randomized to receive **either** a probe drug cocktail consisting of Caffeine (1 tablet à 150mg p.o.), Tolbutamide (1/4 tablet à 500mg (≡ 125 mg) p.o.), Dextromethorphan (10mL syrup à 15mg/5mL p.o.), Digoxin (2 tablets à 0.25mg (≡ 0.5mg) p.o.) Midazolam (2mL solution à 5mg/5mL ≡ 2mg p.o.), **or** Dolutegravir (1 tablet à 50mg p.o). If deemed necessary by the investigator, this may be moved to day -1.
L: BTZ-043 PK sampling (Day 1 and Day 14): blood samples will be taken at 0.0h (pre-dose) and post-dose at 15min, 30min, 1.0h, 1.5h, 2.0h, 3.0h, 4.0h, 6.0h, 8.0h, 10.0h, 12.0h, 24.0h (pre-dose the following day). Time window: 0h – 2h (± 5 min), 3h – 24h (± 10 min)
M: Probe drug PK sampling (Day 0 and Day 14) For BTZ Arm 1-3 only. Will follow the same time points as PK sampling for BTZ.
Please note that for probe drug PK sampling, different blood volumes apply compared to BTZ-043 PK sampling, and that both need to be sampled on day 14.
N: Pharmacogenomics blood sample: single blood sample for possible genetic analysis if consent is given for this on a separate form.
O: Follow-up: This visit may be performed by phone while the Covid-19 pandemic is ongoing, unless there is need to follow up on new complaints reported by the patient, abnormal blood results, clinical assessments or ongoing AE's, that need to be followed-up by physical contact.
P: Ophthalmological Assessment (prior to Day 1 and on Day 15; during follow up as required): this will be carried out by an ophthalmologist affiliated to the sites by referral. The assessment includes history of eye diseases, visual acuity and refractive errors (Snellen Chart), colour vision testing (Ishihara), examination of the pupils, ocular motility and alignment, intraocular pressure, external examination of the eye, slit-lamp examination, fundoscopic examination, optical coherence tomography (OCT). An assessment at visit 18 (Day 22±3) is optional as per recommendation by the ophthalmologist, should there be any ophthalmological AEs or findings on Day 15 or later, that need to be followed up. If the ophthalmological examination falls on a weekend or a public holiday or the ophthalmologist is not available, it should be considered to perform the D15 assessment already either on Day 13, Day 14 or the next working day to come.
Q: After the patient is judged eligible for Stage 2, he will be randomised to one of the study arms and, if applicable, probe drug cocktail or dolutegravir. This randomisation can occur before or on Day 0, in time for administration of the allocated probe drugs.
R: 24h urine collection for determination of host biomarkers for transporter inhibition or metabolites of interest – optional, will be implemented following sponsor decision.

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List of Abbreviations

ADL	Activities of daily living
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
APTT	Activated partial thromboplastin time
ART	Antiretroviral Treatment
AST	Amino aspartate transferase
AUC	Area under the Curve
AV	Atrioventricular
BP	Blood pressure
bpm	Beats per minute
CFU	Colony forming units
CIOMS	Council for International Organizations of Medical Sciences
CMC	Chemistry Manufacturing and Control
CoA	Certificate of Analysis
CrCl	Creatinine Clearance
CRF	Case Report Form
CRM	Continual re-assessment method
CTCAE	Common Terminology criteria for adverse events
DDI	Drug-drug interaction
DLT	Dose-limiting toxicity
EBA	Early bactericidal activity
EBM	Ethambutol
ECG	Electrocardiography
eCrCl	Estimated Creatinine Clearance
eCRF	Electronic Case Report Form
ESR	Erythrocyte sedimentation rate
FDA	Federal drug administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GMP	Good manufacturing Practice
HBsAg	Hepatitis B surface antigene
HCAb	Hepatitis C antibody
HIV	Human immunodeficiency virus
HDPE	High-Density Polyethylen
IB	Investigator's Brochure

ICF	Informed Consent Form
ID	Identification
ICH	International Conference on Harmonisation
INH	Isoniazid
INSTI	Integrase strand transfer inhibitor
IMP	Investigational Medicinal Product
ITT	Intention-to-treat
LAM	Lipoarabinoamman
LLN	Lower limit of normal
LZD	Linezolid
MBLA	Molecular bacterial load assay
MDR	Multidrug-resistant
MIC	Minimum inhibitory concentration
MTB	Mycobacterium tuberculosis
MTD	Maximum tolerated dose
N	Number (typically refers to subjects)
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OCT	Optical coherence tomography
PI	Principal Investigator
PK	Pharmacokinetics
RIF	Rifampicin
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SOE	Schedule of Events
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment emergent adverse event
TSC	Trial steering committee
TTL	Target toxicity level
$T_{1/2}$	Half-life time
ULN	Upper limit of normal
XDR	Extensively drug-resistant
X-ray	Radiography

1. Background Information

1.1 The need for new TB drugs

Whilst progress has been made in recent years in controlling tuberculosis (TB) globally, TB has remained a persistent problem in the developing countries of Africa, Asia and Eastern Europe. TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS [1]. The current first-line anti-tubercular agents have been in use for over 20 years and are relatively ineffective in controlling TB as a public health problem. The long treatment duration and treatment-related toxicity result in poor compliance. As a result of poor treatment compliance, drug resistance is becoming more common. Multidrug-resistant TB (MDR-TB) is a public health emergency, especially in sub-Saharan Africa where human immunodeficiency virus (HIV) infection is endemic. Prevailing challenges such as lack of universal MDR-TB diagnosis, lengthy and toxic treatments that cure only 52% of patients, complicated with development of extensively drug-resistant (XDR) TB, are major impediments in MDR-TB control. Models predict that if the current status is kept up, MDR-TB incidence and associated death trend will increase dramatically and will overturn and become the dominant form of TB by 2050 [2]. Novel approaches to counter-attack the threat are highly needed.
South Africa has a population of 56 million persons and a per capita GDP of $5.273 (US) in 2016. The country has one of the highest TB burdens globally, with a 2016 incidence of 781 per 100.000. 59% of tested patients are HIV positive, which is, as a major risk factor for TB, one of the biggest contributors to the TB epidemic in SA. The frequency of MDR-TB is at 3.4% (95% CI 2.5 4.3) of all newly diagnosed cases, and 7.1% (95% CI 4.8-9.5) of retreatment cases. Unfortunately, MDR-TB and XDR-TB have been on the rise in SA in recent years. In 2016 there were 967 cases of XDR-TB, with 628 cases starting on treatment. So far, the treatment-success in XDR-TB has been approximately 27 [3].

2. Investigational Medicinal Product

2.1 General description of the study drug

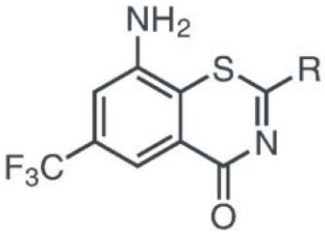
BTZ-043, belonging to the chemical class of benzothiazinones, is a promising new antibiotic for the treatment of tuberculosis. Its mechanism of action is based on the covalent inhibition of a key enzyme involved in mycobacterial cell wall synthesis. In mycobacteria the nitro substituent of BTZ-043 is reduced to a transient nitroso moiety, which then reacts with an essential cysteine residue in the enzyme decaprenylphosphoryl-ß-D-ribose-2'-epimerase (DprE1). DprE1 itself is required for the biosynthesis of decaprenylphosphoryl-β-D-arabinose, an essential component for the cell wall assembly of mycobacteria. Formation of the covalent adduct between BTZ-043 and DprE1 results in inhibition of cell wall biosynthesis and loss of

viability of Mycobacteria Tuberculosis (MTB). Due to this mechanism, BTZ-043 is highly selective for Mycobacteria species (and some other members of Actinomycetales), without affecting the gut flora.

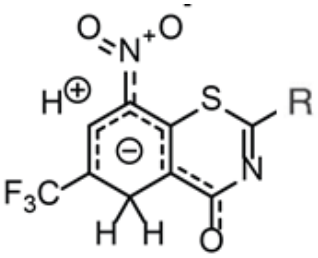
2.2 Metabolism of BTZ-043 in vivo

Figure 1. Major systemic metabolites of BTZ-043

BTZ-045S = M1



Metabolite M2



There are two systemically relevant major metabolites of BTZ-043, which are formed in all species (human, mouse, rat, mini pig). The first metabolite is long known and is termed **BTZ-045S** (**Metabolite M1**). BTZ-045S is formed in microsomal degradation assays, using liver microsomal preparations of human, rat, mouse, dog, monkey, guinea pig, as well as mini pig origin. M1 is 500 times less active against MTB than the parent BTZ-043 [4].

Metabolite M2 is formed by viable blood cells, but not via liver microsomes or hepatocytes. This second metabolite represents a reduced, unstable, de-aromatized Meisenheimer complex [5]. In the presence of atmospheric oxygen, M2 is re-oxidized to BTZ-043. Due to this instability in the presence of oxygen, it is not possible to perform many of the standard metabolite characterisations in vitro. Therefore, no information is available on M2 activity against MTB, nor on M2 potential to interact with drug metabolizing enzymes.

In mice, metabolite M2 proved to be a relatively minor metabolite in plasma. This is in contrast to findings in humans, rats and mini pigs, where M2 strongly dominates over the parent BTZ-043 in plasma (
Table 1). It is not known yet, whether metabolite M2 has biological activity, though it might, in theory, be converted to the nitroso-derivative of BTZ-043 by formal dehydration. First human pharmacokinetic (PK) data are available from a dose-escalation Phase I study of BTZ-043, which allow comparison of human PK parameters with those of the major animal species investigated.

In the following table, BTZ-043 PK values are displayed as BTZ-043, and the sum of BTZ-043 and metabolite M2 (BTZ-043 “total”), after all M2 is re-oxidized to BTZ-043. The BTZ-043 “total” value gives a better understanding of compound absorption and bioavailability, while it is not yet known, which PK assessment will be better related to with efficacy.

Table 1: selected PK parameters for BTZ-043 and main metabolites in Balb/C mouse, rat and human.

		Balb/C Mouse	Female Rat	Human
Dose, day of dosing		250mg/kg, d5	170mg/kg/d, d28	500mg, single dose
PK Index	Unit			
AUC BTZ-043*	[ng*h/mL]	26,600	17,500	2,745
AUC M1*	[ng*h/mL]	n/d	100,000	5,282
AUC M2*	[ng*h/mL]	4,630	91,500	31,237
AUC BTZ-043 "total"*	[ng*h/mL]	31,000	109,000	34147 34,147
Ratio BTZ-043 to M2		5.7	0.2	0.1
Cmax BTZ-043	[ng/mL]	7,030	3,820	1,466
Cmax M1	[ng/mL]	7,030	9,700	295
Cmax M2	[ng/mL]	1,010	10,980	5,329
Cmax BTZ-043 "total"	[ng/mL]			5,857
Ratio BTZ-043 to M2		7.0	0.3	0.3

**$AUC_{0\text{-}inf}$ for Mouse and Human, $AUC_{0\text{-}24}$ for female rat. M1: Metabolite BTZ-045S; M2: Meisenheimer complex metabolite. BTZ-043 "total": measured after complete re-oxidation of M2 to BTZ-043.*

2.3 Previous experience with BTZ-043

2.3.1 Findings from non-clinical studies

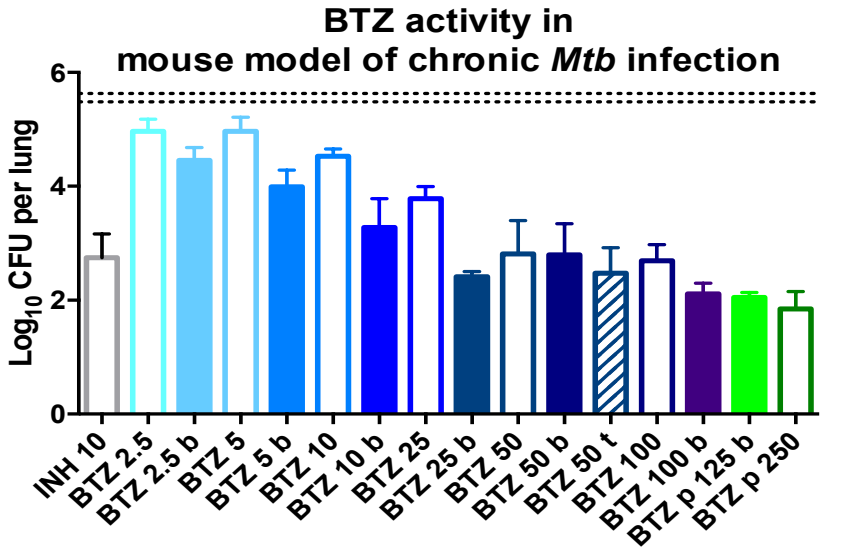
2.3.1.1 Efficacy

BTZ-043 is highly active against a variety of mycobacteria species in vitro (incl. MTB) with minimum inhibitory concentrations (MIC) values in the order of 0.1 – 8 ng/mL, also in infected macrophages.

Among primary patients' isolates of MTB, no baseline rate of BTZ-043 resistance was identified so far, even in extensively resistant strains. When resistance was artificially generated in laboratory strains, it was generally due to mutations of DprE1, where Cys387 was replaced by Ser or Gly codons. Resistance to other anti-tuberculosis drugs did not confer cross-resistance to BTZ-043. Thus, BTZ-043 is suitable for treatment of drug-resistant MTB.

In vivo, BTZ-043 efficiently inhibits growth of MTB strain H37Rv in mice at doses from 2.5 mg/kg upwards (Figure 2). Activity increases up to dose levels of 250 mg/kg and reaches a plateau then; although doses between 25 mg/kg – 100 mg/kg induce an almost as strong bactericidal effect as 250 mg/kg).

Figure 2. Dose-response observations in Balb/C mice



b: given twice daily t: given three times daily.
(Nuermberger E,[4])

2.3.1.2 Secondary pharmacology

Vasopressin receptor V1a (antagonistic interaction) and acetylcholine esterase (enzyme inhibition) could be identified as definitive secondary targets for BTZ-043. The muscarinic acetylcholine receptor M1 (antagonistic interaction) may also be a potential secondary target for BTZ-043. Metabolite BTZ-045S was identified as another potential antagonist of muscarinic acetylcholine receptor M1, but no interaction for vasopressin receptor V1a and acetylcholine esterase was found for M1. The secondary targets may potentially be associated with adverse effects on vital functions. Therefore, models were developed to allow an estimation of systemic BTZ-043 concentrations leading to 10% and 50% receptor occupancy in the presence and absence of plasma proteins. According to these models, off-target interactions, at least with the vasopressin receptor V1a and acetylcholine esterase, must be taken into account during realistic clinical exposure scenarios.

Adverse neurological reactions that might possibly be linked to an interaction of BTZ-043 with acetylcholine esterase were seen in a modified Irwin Test in rats at an oral dose level of 470 mg/kg (see below).

The nonclinical database does not indicate any antagonistic interaction of BTZ-043 with the vasopressin receptor V1a (i.e. no hypotension), neither does the clinical database. An antagonistic interaction of BTZ-043 with muscarinic acetylcholine receptor M1 can also not be identified in the nonclinical database. However, in a Phase I study of BTZ-043 a slight transient increase of blood pressure after doses of 125mg, 250mg and 500 mg was observed, together with a slight increase of heart rate after doses of 500 mg. These effects might be linked to an antagonistic interaction of BTZ-043 with muscarinic acetylcholine receptor M1, although in

vitro receptor occupancy data and IC50 data do not imply such an effect during realistic clinical exposure scenarios.
Notably, no effects at relevant concentration levels of BTZ-043 were observed on human ether-à-go-go-related gene (hERG) tail currents. In rats, a single oral administration of BTZ-043 up to a dose of 200mg/kg was not associated with substantial physiological effects on the respiratory parameters.
BTZ-043 did not interact in terms of efficacy with rifampicin, isoniazid, ethambutol, pretomanid, moxifloxacin, and meropenem. However, synergy was seen with the diarylquinoline antibiotic bedaquiline. The combined effectiveness of bedaquiline and BTZ-043 may offer an attractive basis for a new tuberculosis regimen, especially when rifampicin and isoniazid cannot be used in situations such as multidrug resistant tuberculosis, drug toxicity, or interaction of rifampicin with antiretroviral drugs.

2.3.2 Excretion

The routes and rates of excretion of BTZ-043 and its metabolites have been investigated in a mass balance study in rats using 14C-labelled BTZ-043. Results from the per os (p.o.) arm the 14C-BTZ-043 absorption, and excretion study in rats indicated, that 46.3 ± 8.78% of drug-related radioactivity was eliminated into urine and 48.8 ± 13.6% into faeces during 168 h after dosing. The recovery of total radioactivity in excreta over 168 h was 95.3 ± 14.6%. Results from the intravenous (i.v.) arm of this study indicated, that 44.4 ± 4.89% of drug related radioactivity is eliminated into urine and 44.5 ± 5.25% into faeces during 168 h after dosing. The recovery of total radioactivity in excreta was 89.2 ± 3.71%. The AUC0-t/Dose for total radioactivity was 7330 h*ng/mL (i.v.) and 2720 (p.o.), suggesting an oral bioavailability (Fa0-t) of only 37.1%. However, following i.v. dosing (drug is 100% available), urinary excretion was 44.4%. After p.o. dosing, urinary excretion was with 46.3% about the same, suggesting that BTZ-043 and its metabolites are completely absorbed. This is not in line with the calculated absorption based on plasma PK data and indicates differences of elimination of radiolabelled BTZ-043, depending on the route of administration. Most probably, a distinct first pass effect is involved.
In the same context, after single oral administration of 100 mg/kg BTZ-043 to bile duct-cannulated male Wistar rats, the drug was excreted into bile and urine in an extensively metabolized form. The minimal absorbed amount of BTZ-043 was estimated in this study to be about 40%. About 13% of the dose was found in bile and about 27% in urine mainly as Phase I and Phase II metabolites. Thus, the renal route of excretion is the more dominant route, at least within the boundaries of this study in rats.

2.3.3 Potential Drug-Drug-Interactions

No stand-alone pharmacokinetic interaction studies were conducted in humans. One study in mini pigs showed, that pre-treatment with the H2-receptor antagonist famotidine (in order to

increase the gastric pH-level) decreased BTZ-043 bioavailability; therefore antacid drugs will be excluded as concomitant medications in this study.
In vitro, BTZ-043 did not inhibit CYP 1A2, 2B6, 2C8, 2C19, 2D6 and 3A4 (testosterone) up to concentrations of 10 µM. BTZ-043 produced a minor inhibition in the order of 20 – 25% against CYP2C9 at 10 µM. Furthermore, increased metabolism of midazolam by CYP3A4 was observed at BTZ-043 concentrations of 10 µM.
The potency of the metabolites for inhibiting or inducing drug metabolizing enzymes is difficult to fully assess in vitro, due to the instability of M2. We therefore opted to assess the interaction potential of BTZ-043 and its metabolites in humans in this study, by using a probe drug approach, as recommended by U.S. FDA in their daft guidance issued 2017, on *"Clinical Drug Interaction Studies — Study Design, Data Analysis, and Clinical Implications; Guidance for Industry"*.
We will examine the potential of BTZ-043 and it´s in vivo generated metabolites as perpetrators, to inhibit or induce the following drug metabolising enzymes and influence the activity of P-glycoprotein. We will use the following FDA-recommended probe drugs, which are specific substrates for the following enzymes:

- CYP1A2: caffeine
- CYP2C9: tolbutamide
- CYP2D6: dextromethorphan
- CYP3A: midazolam

To assess any influence on p-glycoprotein, digoxin will be used as a substrate.

In addition, to enable a combination of BTZ-043 with dolutegravir as the most likely future backbone of antiretroviral treatment in following trials, some patients in stage 2 will receive dolutegravir, before BTZ-043 and at steady state, in order to perform an exploratory assessment of BTZ-043's influence on dolutegravir PK. This is necessary, since the metabolism of dolutegravir occurs via UGT-transferases, which are not covered by the probe drugs above.

To complement drug–drug interaction risk assessment, the most appropriate endogenous biomarker(s) and/or metabolites of interest, may be investigated in plasma and/or urine.

2.3.4 Pharmacokinetics in preclinical species and humans

Several analytical procedures have been developed to measure concentrations of BTZ-043 and its major metabolites BTZ-045S (M1) and M2 in biological samples. First human pharmacokinetic data are available from a dose-escalation Phase I study of BTZ-043, which allow comparison of human PK parameters with those of the major animal species investigated, as shown in

Table 1.

2.3.4.1 BTZ-043 (parent compound)

Oral PK studies of BTZ-043 in smaller species, like mice and rats, revealed rapid oral absorption of BTZ-043 with t_{max} in the order of 15 – 40 min and $t_{1/2}$ in the order of 1.2 - 1.5 h. In larger species, such as mini pigs, BTZ-043 also showed fast absorption (t_{max} in the order of 1 – 1.5 h) as well as relatively rapid elimination with terminal $t_{1/2}$ in the order of 1.5 - 2 h. In humans, absorption again was rapid, with a median t_{max} 0.5 to 0.75 hours after dosing.
In humans, geometric mean $t_{1/2}$ was short (about 1.1 to 2.0 hours). After administration of higher doses of BTZ-043, a second small peak (possibly related to enterohepatic circulation) was observed.

2.3.4.2 BTZ-045S (M1)

The metabolite BTZ-045S has a longer terminal $t_{1/2}$ in rats and mini pigs (> 6 hours) compared to the parent. Among all species examined, rats showed the highest ratio of M1 to parent. AUCs of BTZ-043 "total" and M1 were in similar orders of magnitude.
In humans and mini pigs, M1 is substantially less abundant. Peak concentrations and AUCs of M1 were only around 20%of the peak concentrations and AUCs of the BTZ-043 "total" in humans. Peak concentrations were reached at 7.0 – 8.4 hours after dosing. Thereafter, concentrations of BTZ-045S slowly decreased, with a geometric mean $t_{1/2}$ in the order of 8.4 to 9.0 hours.

In line with the slower excretion of M1, some accumulation was seen in female rats after repeated dosing. A tendency of sex-dependent BTZ-045S disposition was also observed in rats, with female rats achieving higher concentrations. In contrast, male mini pigs had higher concentrations of M1 than females. In humans, no significant effects of sex whatsoever were identified in the PK dataset.

2.3.4.3 M2 (Meisenheimer complex)

Metabolite M2 showed similar kinetic properties to those of BTZ-043 in rats, mini pigs and humans. In humans, M2 peak concentrations were observed very shortly after M0 peak concentrations. In all three species, not in mice though, the absorbed test item was dominantly present in the circulation as metabolite M2.
In humans, peak concentrations of Metabolite M2 were 3 – 5 fold higher than those of the parent BTZ-043, indicating rapid transformation of BTZ-043 to M2.

2.3.4.4 Dose-exposure relationship in humans

While the AUC of **BTZ-043 i**ncreased slightly more than dose-proportionally from the 125 mg to the 500 mg dose (slope of about 1.4), the slopes of the regression curves for AUC and C_{max} of **BTZ-043 "total"** were nearly '1' (slope of AUC about 1.1, slope of C_{max} of 0.9 with 90%

confidence intervals including the '1'), giving an indication for a dose proportional increase in overall exposure to the compound.

2.3.4.5 Organ distribution

Organ distribution data of BTZ-043 have been generated in a quantitative whole body autoradiography study using 14C-BTZ-043 in rats. Following a single oral dose of 60 mg/kg, total radiolabelled components were distributed extravascularly throughout the body. For all tissues, C_{max} was reached between 0.5 and 4 hours post-dose, except for intestinal wall (colon) and urinary bladder wall with C_{max} values at 8 hours each. In the majority of tissues, total radioactivity concentrations were lower as compared to blood radioactivity concentrations. An AUC0-t ratio (tissue:blood) of >1 was found only in the urinary bladder wall, intestinal wall (colon), eye (ciliary body), liver, eye (choroid), kidney (total), intestinal wall (small intestine), blood vessel wall, nasal mucosa and hair follicle. All remaining tissues had an AUC0-t ratio (tissue:blood) of <1. Concentrations of radioactivity in brain were generally low, amounting to 1/5 of blood concentrations in terms of C_{max} and 1/10 in terms of AUC0-t. The longest terminal $t_{1/2}$ values (>10 hours but <108 hours) were observed in the following tissues in decreasing order: Eye (choroid), eye (ciliary body), nasal mucosa, liver, blood vessel wall, prostate, meninges (choroid plexus) and kidneys (total). For all other organs/tissues, $t_{1/2}$ ranged from 1.33 hours to 8.97 hours. Radioactivity was still observed in the intestinal content at the last time point (168 hours after dosing).

2.3.5 Toxicology

2.3.5.1 Toxicology studies in non-rodents: mini pigs

The mini pig was chosen as the non-rodent toxicology model, since attempts to use dogs did not result in achievement of sufficient plasma levels after oral dosing, while this was possible in mini pigs.

No stand-alone single dose toxicity studies of BTZ-043 have been performed. However, a dose escalation study of BTZ-043 in mini pigs was conducted to determine the maximum tolerated dose (MTD) of BTZ-043 for later repeated dose toxicity studies in this species. The MTD was not reached during dose escalation up to the maximum dose level of 1000 mg/kg.

In a 7-days oral repeated dose range finder in mini pigs, repeated oral treatment with 360 mg/kg of BTZ-043 over 7 days was considered in range of the MTD. Small microscopic changes (i.e. haemorrhages) in a variety of visceral organs were not regarded as treatment-related, since the same pattern of microscopic changes was also observed in all dose groups as well as in the vehicle control group of the later pivotal 28-days toxicity study of BTZ-043 in mini pigs. In a pivotal subacute (28-days) study in mini pigs, BTZ-043 was exceptionally well tolerated. BTZ-043 administered orally at 3 dose levels (40, 120 and 360 mg/kg) to mini pigs once a day over a period of 28 days resulted in no adverse effects. The 360 mg/kg dose level is therefore considered to be the No-Observed Effect Level (NOEL) in mini pigs.

In all mini pig studies, no test item related effects on blood pressure, heart rate and ECG parameters nor clinical symptoms were observed up to a high dose level of 360 mg/kg.

2.3.5.2 Toxicology studies in rats

In a 14-days oral repeated dose range finder study in rats, orally administered BTZ-043 was well tolerated by male rats up to the maximum dose level of 600 mg/kg/day. Female rats appeared to be more sensitive to toxicity by BTZ-043. In female rats, orally administered BTZ-043 was well tolerated up to the dose level of 270 mg/kg/day.

In a pivotal subacute (28-days) study in rats, administration of BTZ-043 by oral gavage at daily doses of 60, 170 and 470 mg/kg for 28 consecutive days was associated with noteworthy effects only at the highest dose level of 470 mg/kg. In few females a treatment related observation was made in the Irwin test at 2 h and 4 h after the treatment on day 28 (in 2 - 4 of 8 animals). In the affected females the main findings were: decreased values in arousal, body position, body tone, plantar reflex, grip strength and responses to finger approach, head touch, fear and startle and an increase in positional passivity/catalepsy and difficulty to right up. 2 females showed decreased body temperature.

Other effects were mostly related to an increased liver weight, combined with increased AST and ALT activity. However, no microscopic findings considered related to the test item were observed in any of the examined organs and tissues. Observed effects were generally more pronounced in female than in male rats. All observed effects were reversible and disappeared during the recovery period. The no observed adverse effect level (NOAEL) for BTZ-043 in this study over 28 day was considered to be the second highest dose of 170 mg/kg bw/day.

In a pivotal sub chronic (6-months) study in rats, administration of BTZ-043 by oral gavage at daily doses of 60, 130 and 380 mg/kg for 26 Weeks was well tolerated. Most noteworthy findings were related to the adrenals and the liver. Statistically significant test item-related changes of organ weights were observed in the liver for the absolute and relative (to body and brain) weight in the high dose male and in the high and mid dose female animals. Furthermore, high dose females showed a test item-related increased incidence of enlarged adrenals. These changes can be considered as signs of increased metabolic activity of the liver. All of these changes are considered as non-adverse.

Toxicokinetics showed some sex-dependent differences. In general, the plasma concentrations were higher in females than in males.

The NOAEL in this study was determined to be 380 mg/kg bw/day (high dose) for both sexes.

These toxicological animal studies in sum showed a very benign toxicological profile of BTZ-043. All clinical signs observed in the high dose groups disappeared on the first day of the recovery period without drug administration. All adverse effects observed in the pivotal subacute (28-days) study in rats were reversible.

Onset of BTZ-043-derived adverse effects was observed to be slowly progressing and well controllable. The high NOAEL of 380mg/kg bw over 6 months in rats indicates, that the drug will most likely be well tolerated over the duration of the standard TB treatment duration.

2.3.6 Findings from clinical studies

BTZ-043 has been clinically tested in a Phase I study between June and August 2018, assessing safety and tolerability of single escalating doses of BTZ-043.

The primary objective of this study was, to evaluate the safety and tolerability of orally administered BTZ-043 in a dose range around a likely therapeutic dose, as measured by clinical observations, vital signs, safety laboratory and ECG assessments. Secondary objectives included the description of the PK of BTZ-043 after a single dose, the description of the effect of sex differences on systemic exposure and the assessment of the pro-arrhythmic risks of BTZ-043, using triplicate 12-lead ECG monitoring.

During this study, BTZ-043 was given to 24 healthy male and female subjects. Single doses of 125 mg, 250 mg and 500 mg BTZ-043 were administered to 8 subjects each, while 6 subjects received placebo. No further dose increase was performed because the predefined target exposure of 43.850 ng*h/mL BTZ-043 was achieved.

Single oral doses of 125 to 500 mg BTZ-043 were safe and well tolerated. There were no SAEs and no subject discontinued the study due to AEs. All treatment emergent adverse events (TEAEs) were of mild or moderate intensity without apparent differences between male and female subjects. Most TEAEs started within 30 minutes after dosing and were of short duration.

The most frequently reported TEAEs were nervous system disorders (dizziness and headache) reported by overall 11 subjects: 1 subject each (12.5% and 16.7%) after 125 mg BTZ-043 and placebo respectively, 5 subjects (62.5%) after 250 mg BTZ-043 and 4 subjects (50.0%) after 500 mg BTZ-043.

This was followed by vascular disorders (hypertension and hot flush), reported by overall 7 subjects: 1 subject (12.5%) after 125 mg BTZ-043 and 3 subjects each (37.5%) after 250 mg and 500 mg BTZ-043, respectively. No vascular disorders were reported after placebo.

Among the vascular disorders, hypertension was reported as AE for 5 subjects: 1 subject after 125 mg BTZ-043, three subjects after 250 mg BTZ-043 and one subject after 500 mg BTZ-043. There was no apparent dose-response relationship in the number of subjects experiencing a clinically relevant blood pressure increase (see Investigator's Brochure, Table 33).

A mild increase in mean systolic and diastolic blood pressure was observed after administration of 250 mg and 500 mg BTZ-043 at 0.5 to 1 hour after dosing (maximal systolic increase of 10.0 and 12.1 mmHg, respectively, compared to pre-dose, for 125 mg BTZ-043 and placebo a maximal increase of 2.4 and 4.8 mmHg was observed). Mean pulse rate decreased in all treatment groups after dosing compared to pre-dose, except for the 500 mg group, which showed an increase of up to 11.0 bpm at 1 hour post-dose.

Triplicate 12-lead ECG monitoring demonstrated no apparent relationship between heart rate corrected QT (both QTcB and QTcF) and the plasma concentration of BTZ-043. Mean QTcF

showed a mild increase after dosing of BTZ-043, compared to pre-dose, similarly for all 3 active doses (increase of 3.08 to 4.84 ms at 1 to 4 hours after dosing, no increase after placebo dosing). No QTcF-/QTcB-values >450 ms nor increases of >30 ms were recorded in individual patients.
In expanded neurological examinations no changes after dosing were found.
ICH M3 was followed to set an exposure (PK) threshold for stopping of dose escalation in healthy volunteers/exploratory studies [6] at ½ of the AUC (mean of male and female animals) at NOAEL in the more sensitive animal species (rat) at a maximum AUC_{0-24} of more than 43.850 ng*h/mL BTZ-043 "total". Dose-exposure analysis suggested, that this threshold would have been surpassed with a dose increase beyond 500 mg; therefore, higher doses will have to be tested in patients

Interim safety data from Stage 1b/2a of The PanACEA-BTZ-043-02 study, after a total of 24 participants has been enrolled and dosed over 14 days with BTZ-043 in a dose range of 250-1750 mg, show the following findings:
BTZ-043 turned out to be safe and well tolerated within the applied dose range. No drug related SAE or grade 3 AE was observed. All grade 1 and 2 AEs completely resolved.
The following grade 1 and 2 AEs with at least possible drug related causality according to investigators assessment were observed during stage 1 of the study:
The most frequent reports were observed for the gastrointestinal system. 6 study participants complained about unspecific abdominal pain, nausea and vomiting.
The next frequent AE was dizziness or light-headedness, which was reported by a total of 4 study participants. In 3 participants, elevated liver enzymes were recorded as AEs with possible correlation. In all of these participants, the values were decreasing latest after four days during continuous treatment with BTZ-043 and were back to normal at the level observed during screening until the end of treatment or at follow-up.
2 participants experienced vision disturbances such as intermittent blurred vision or decreased vision acuity. This was followed up within an examination by a specialized ophthalmologist. None of the participants showed abnormalities at the eyes including the retina and the optical nerve. Visual impairments resolved in both participants until follow-up.
2 persons reported generalized pruritus or localized urticarial and 1 person had an increased blood pressure at times. Further, 1 person had a minor epistaxis.

Initially, dose escalation was planned with doses up to 2000 mg. The TSC decided not to enrol cohort 8 with a daily dose of 2000 mg as the available data from the interim analysis showed no further increase in exposure nor in bactericidal activity from cohort 5 on.

2.4 Summary of known and potential risks of the IMP used in this study

2.4.1 BTZ-043: known and potential risks

BTZ-043 was exceptionally well tolerated in toxicity studies in animals.
In preclinical good laboratory practice (GLP) animal toxicology studies, conducted in rats for up to 6 months and in mini pigs for up to 28 days of dosing, BTZ-043 was found to be safe and well tolerated up to high doses, with NOAELs of 380 mg/kg (rat) and 360 mg/kg (mini pig). Both being the highest tested doses in those studies.
In a shorter 28-day study in rats, which tested up to 470mg/kg, an abnormal Irwin test was observed at the highest tested dose of 470 mg/kg in female rats. The abnormality was not severe and reversible the day after the last dosing.
Exposure to both, BTZ-043 and M1, was exceptionally high in these female rats, and evidence for accumulation over the 28 days of dosing was seen.
All other observed adverse effects in rats were reversible the day after the last treatment as well.
In humans, BTZ-043 is unlikely to accumulate during repeated dosing, given the very rapid absorption and the short half-lives of not more than 3.7 h for BTZ-043 “total”.
M1 clearance though is slower and a slight accumulation might occur in repeated dosing in humans. A mean accumulation ratio of 1.19 for M1 has been calculated from the Phase Ia PK data.
However, given the observation that M1 exposure is several fold lower in humans than it is in rats, both, in absolute concentrations and in relation to the exposure of the parent, it is highly unlikely, that this will cause a clinical effect.
No effects at relevant concentration levels of BTZ-043 were observed on cardiovascular parameters in nonclinical studies.

In the Phase I trial in humans all AEs were of mild to moderate intensity and of short duration. Mean systolic blood pressure increased slightly after administration of 125, 250 mg and 500 mg BTZ-043. Clinically relevant (grade 2) blood pressure increase was seen in 5 participants, but there was no increase in the proportion of participants experiencing this event with increasing dose, nor in the severity of individual events. The observed transient elevation of blood pressure in humans can be well monitored and can be controlled easily in case of medical indication (if rising above the stopping criteria).
There were no considerable treatment related differences in mean ECG parameters. None of the observed cardiovascular changes was severe.

Thus, inclusion of standard cardiovascular monitoring (BP, ECG) and definition of adequate thresholds for BP increase to stop dosing, appears to be sufficient for forthcoming early human trials of BTZ-043.

Further, the planned dose escalation steps of an absolute increment of 250 mg in our study are small, and so far, exposure has been proportional to dose.

Following subjective temporary visual disturbances with normal findings in the ophthalmology assessments in two patients in Phase 1b/2a, the trial steering committee decided that from 24 August 2020 onwards, patients in the BTZ-043-02 study should have two mandatory ophthalmologist visits, one during screening (prior to day 1) and on day 15, in order to achieve better standardization of assessments.

2.5. Summary of known and potential risks of other drugs used in this study

For clarity, all licenced drugs in this study (all drugs other than BTZ-043), are referred to as ´non IMP study drugs´. When reference is made to ´study drugs´, all drugs including BTZ-043 are meant.

Rifafour® e-275 (or equivalent)

The drugs **Rifampicin, Isoniazid, Pyrazinamide and Ethambutol** will be administered within the standard 4-drug regimen as Rifafour® e-275. Please see the Package Insert for Rifafour® e-275 for its known and potential risks and benefits. The package insert for a formulation marketed in South Africa has been provided as an example for an insert following South African regulations (Appendix 1. Package Insert RIFAFOUR®e-275 TABLETS, page 100).

To minimize the risk for the patients, patient's safety will be monitored frequently by physical examination, evaluation of vital signs and assessment of adverse effects during the treatment phase and at follow-up. At regular intervals, samples will be collected for serum chemistry, haematology and urinalysis, and 12-lead ECGs will be performed.

Probe Drug Cocktail

In this study several drugs will be administered orally in a single, low dose as probe drugs to assess the activity of metabolizing enzymes and drug transporters in the context of 'phenotyping'.

Phenotyping is defined as measuring the *in vivo* activity of an enzyme or transporter in an individual [7]. It is performed by single administration of a selective substrate for the enzyme or transporter (a 'probe' drug) followed by determination of a phenotyping 'metric'. The metrics used are pharmacokinetic measures such as exposure of the probe drug, its clearance or ratios of metabolites over parent probe drug concentrations in plasma, saliva or urine.

Probe drugs or phenotyping agents are *'products used to assess end-points in the clinical trial'*, which are given to the subject as a tool to assess a relevant clinical trial endpoint; they are not being tested or used as a reference in the clinical trial.

The probe drugs are depicted in the table below. Tolbutamide is not registered for use in South Africa and will be provided by the Department of Pharmacy of the Radboudumc, Nijmegen, The Netherlands.

Table 2. Probe Drug Cocktail Agents

Agents	Dose	Registered formulation	Goal
Caffeine	150 mg	Tablet 150mg	Probe for CYP1A2
Tolbutamide	125 mg	Tablet 500 mg	Probe for CYP2C9
Midazolam	2 mg	i.v. Solution to be given orally 1mg/1mL	Probe for CYP3A4
Dextromethorphan	30 mg	10mL syrup 15mg/5mL	Probe for CYP2D6
Digoxin	0.5 mg	Tablet 0.25 mg	Probe for P-gp

2/3 of the participants in BTZ Arms 1-3 will receive a cocktail of phenotyping agents at days 1 and 14. The composition of this cocktail is based on recommendation of the U.S. FDA, and on studies performed by the group of Prof. Fuhr (Department of Pharmacology, University of Cologne, Germany Cologne, Germany) [8]. The administered doses of the phenotyping cocktail, containing Caffeine, Tolbutamide, Dextromethorphan, Digoxin, Midazolam (Cologne Cocktail) agents did not exceed therapeutic doses in these studies. Administration was safe and well tolerated [8, 9]. No changes in physical examinations, vital signs, clinical safety laboratory parameters or electrocardiograms, have been observed in the studies conducted thus far using variants of the Cologne cocktail. No hypoglycaemic effect was seen by the low 125mg tolbutamide dose for this cocktail.
To minimize the risk for the patients, patient's safety will be monitored frequently by physical examination, evaluation of vital signs and assessment of adverse effects. At regular intervals samples will be collected for serum chemistry, haematology and urinalysis.

Dolutegravir
1/3 of the participants in BTZ Arms 1-3 will receive Dolutegravir as probe Drug. Raltegravir, elvitegravir and dolutegravir are currently the only drugs in the INSTI drug class to receive approval for the treatment of HIV-1 infection. There have been reports of hypersensitivity reactions, rashes, and liver enzyme elevations for the use of dolutegravir, as well as psychiatric events, like depression. Dolutegravir might cause serum creatinine kinase elevations and decreased renal tubular secretion of creatinine, leading to small increases in serum creatinine.
To minimize the risk for the patients, patient's safety will be monitored frequently by physical examination, evaluation of vital signs and assessment of adverse effects. At regular intervals samples will be collected for serum chemistry, haematology and urinalysis, and 12-lead ECGs will be performed.
Please see the Package Insert for dolutegravir for its known and potential risks and benefits. The package insert for a formulation marketed in South Africa has been provided as an

example for an insert following South African regulations (Appendix 2. Package Insert Dolutegravir, page 104).

3. Rationale for the Study

New TB treatment regimens are vital to combat the TB epidemic and, most importantly, the drug-resistant TB epidemic.
In MDR-TB, only 52% of MDR cases achieve cure [1]. A model of MDR-TB in Vietnam showed that under current diagnostic and treatment practices, MDR-TB incidence will increase by 17%, and deaths by 22%, within ten years [10]. In a similar model in China, MDR-TB will become the dominant form of TB by 2050 [11].
To effectively combat this epidemic, more potent drug combinations with regard to sterilizing capacity are necessary. These can be created through introduction of novel drugs with a low pre-existing resistance.
BTZ-043, belonging to the chemical class of benzothiazinones, is a promising new antibiotic for the treatment of tuberculosis. PanACEA developed the concept of this BTZ-043 dose selection study to evaluate the safety, tolerability, extended early bactericidal activity and PK of different doses of BTZ-043 at this stage to identify the possible doses for the following investigations of anti-TB drug combinations, including BTZ-043, in the next study.

This study employs a dose escalation design in stage 1, which is commonly used in industry and will generate safety and PK information during 14-day repeated dosing with as little delay as possible. Dose escalation in stage 1 will be at fixed increments of 250 mg, less than proportional. The dose range to be explored has been chosen based on the observation that the metabolite M2 in humans represents a large proportion of the exposure to BTZ-043 “total” while it only minor contributes to the exposure of BTZ-043 “total” in mice, where dose-response data were generated. So far, it was not feasible to generate in vivo activity data of M2, as the mouse represents the only well characterized preclinical model of TB infection. Due to the instability of M2 towards atmospheric oxygen and subsequent oxidation to BTZ-043, in vitro assays with the metabolite are not feasible. Should M2 be inactive and the anti-microbial activity of BTZ-043 depend on the parent compound, an exploration of higher doses will be necessary to achieve effective plasma levels of the parent compound similar to those found in mice. (
Table 1). Moreover, as recent clinical studies by the PanACEA consortium showed, that Rifampicin is significantly more effective in higher than standard doses whilst being safe, which shows that rifampicin has been used at the wrong dose for decades [12] , the dose escalation to the maximum feasible dose of 2000 mg is intended to prevent suboptimal doses of BTZ-043 and the subsequent development of resistance.
The result of stage 1 will be a safe therapeutic window of doses. In stage 2, within this predefined window, this trial will collect data in a higher number of patients on safety of the

given doses in a prospectively randomized approach; but it also aims to describe an exposure – response relationship and a dose-response relationship for bactericidal activity observed. Additionally, a split-dose administration to evaluate possible beneficial effects on BTZ-043 efficacy compared to single dose administration may be evaluated in the optional additional arms 5, and 6 that may be added to stage 2. Total daily dose in any case will not exceed the dose range proven safe and effective in stage 1.

4. Study Objectives

4.1 Primary Objective

The primary objective is to assess the safety and tolerability of BTZ-043 given once or twice daily over 14 days by evaluation of AEs during treatment and follow-up period in patients with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary tuberculosis by evaluating AEs during treatment- and follow-up phase including:

- Clinical observations
- Vital signs
- Serum chemistry, haematology and coagulation parameters with
  - baseline measurements
- ECG, incl. heart rate, PR interval, QRS, QT interval, QT interval corrected for heart rate using Fridericia´s correction, (QTcF); change of QTcF from baseline to post-dose measurements; morphological abnormalities.

4.2 Secondary Objectives

The secondary objectives of this study are the following:

1. Secondary bactericidal activity objective:

To evaluate the bactericidal activity of different doses of BTZ-043, given once or twice daily over 14 days, by investigating the change in viable mycobacterial load in liquid and on solid culture LAM load and mycobacterial RNA load (molecular bacterial load assay, MBLA) in sputum over time between day -1 and day 15.

2. Secondary pharmacokinetic objectives:

a) To describe the PK of BTZ-043 and its major metabolites BTZ-045S and M2, and other metabolites of interest after a single or split dose and at steady state
b) To analyse the population PK of BTZ-043 and its main metabolites to quantify inter-individual variability, suitable for evaluation of alternative dosing regimens
c) To determine the effect of a high-fat high-calorie meal on exposure by evaluating the PK of BTZ within 24 hours after fasting intake of BTZ-043 vs. intake after a defined high-caloric meal at steady state (stage 1)

d) To assess the effect of BTZ-043 on the activity of hepatic CYP 450 enzymes, P-glycoprotein, and the metabolism of dolutegravir, as measured by accelerated versus inhibited metabolism of either a pre-defined probe drug cocktail or of dolutegravir (stage 2)
e) To complement drug–drug interaction risk assessment via investigation of appropriate endogenous biomarker(s) from blood or urine samples.

5. Study Design

5.1 Summary

This is a prospective, open label, two-centre, randomized, controlled, assessor/observer-blinded, two-stage, phase Ib/IIa-study to evaluate the safety, tolerability, PK and bactericidal activity of eight different doses of BTZ-043, administered orally once daily over 14 days in the 1st stage and to evaluate the safety, tolerability, PK with the goal to define a safe therapeutic window for BTZ-043. Within this window, three doses will be chosen to generate additional safety data and to assess the dose dependent bactericidal activity of BTZ-043, administered orally once or twice daily over 14 days, compared to standard treatment in participants with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary tuberculosis.
We will enrol a total of up to 105 (see section 7.4, male and female patients, aged 18 years and older up to 64 years, with newly diagnosed, uncomplicated, smear-positive, drug-susceptible pulmonary tuberculosis in two stages.

In the case of unforeseen delays or a rate of dropouts or non-evaluable participants that is higher than anticipated during the 1st stage, it may be necessary to recruit more participants than planned into the entire study, to be able to reach the anticipated sample size for the 2nd stage of the trial (see Sample size determination, page 86).

Stage 1
The aim of stage 1 is, to define the safe therapeutic window for BTZ-043. In order to achieve this most effectively we will enrol patients sequentially in cohorts of 3 patients. Patients in the first cohort will receive the lowest dose of 250mg of BTZ-043 for 14 days.
The continual reassessment method (CRM) described in Zhou et al, 2003 [13] (see below), will be used to provide statistical guidance to the TSC for dose escalation, although the TSC will have final say.

After the third patient of each cohort has completed at least 7 days of dosing or earlier, in exceptional cases a dosing recommendation for the next cohort will be made using the CRM algorithm and the TSC will meet for a dose escalation meeting. All available data, in particular safety data, from current and prior cohorts (up to and beyond 7 days where available) will be reviewed at the dose escalation meeting. Although the CRM algorithm will be used to

recommend the next dosing level, the TSC will make the final decision and can halt the study or halt or de-escalate dose escalation as appropriate at any time during the trial.

The CRM design was first developed nearly 30 years ago and has been widely used in many disease areas across the globe [14]. It is a type of Bayesian adaptive dose escalation design that assumes a two-parameter logistic model for the toxicity rate based on dose. It is a modified version of the original Continual Reassessment Method (CRM) [15]. The design using a statistical model for dose and toxicity, and is expected to locate the dose with target toxicity level (TTL) efficiently while minimizing the number of patients exposed either to doses that are unsafe or are too low to merit further evaluation. The method is fully adaptive and makes use of all the dose limiting toxicity (DLT) information available at the time of each dose assignment, unlike other designs for dose finding in TB trials that are less efficient are require more participants [12, 16].
The CRM algorithm will not recommend increasing the dose by more than 250mg (maximum dose increment), in other words no discrete dose level will be skipped.
Dose limiting toxicities have been defined at an expert meeting (see AE definitions).

In this study we aim to identify the dose that results in no more than 10% of DLTs during 14 days of treatment. This is the target toxicity level (TTL).
At the time of each dose escalation meeting, all available data on DLTs will be included in the CRM model and the algorithm will be used to obtain posterior probabilities of occurrence of DLT at each discrete dose level. The recommended doses will be the highest dose with posterior probability of DLT less than 10%, or the next discrete dose in sequence (250mg, 500mg, 750mg, 1000mg, 1250mg, 1500mg, 1750mg and 2000mg), whichever is lower. The TSC will be presented with the recommended next dose level from the algorithm in addition to the updated dose-toxicity curve. Note that de-escalation as well as escalation is possible using this method, and the TSC always makes the final decision.

Stage 2
During the second stage, patients will be randomized to receive either one of three doses of BTZ-043 within the therapeutic window defined in stage 1, or the control regimen of daily doses of Rifafour e-275® (or equivalent)., adapted to body weight and given according to the South African Guidelines for TB-treatment [7], for 14 days in the ratio 3:3:3:2. The choice of doses of BTZ-043 in the second stage will be decided by the TSC and will be chosen to allow a range of safe doses to demonstrate a relationship between bactericidal activity and dose, and also with pharmacokinetic exposure. After an interim analysis of the first patients in the BTZ arms, it will be decided whether any arms will be added, and if so, which dosage(s) will be given, and whether one or both arms will receive once daily or split dosing to make up the total daily dosage decided earlier. Arms 1-4 of Stage 2 will be completed once the total number enrolled (across all arms and both stages) reaches 77. If the TSC decides for additional dose

groups of BTZ-043, the total number of enrolled patients in the study will be increased to up to 105.

Randomization will be implemented using sequentially numbered opaque envelopes that contain the allocated treatment arm and will only be opened once eligibility has been verified and immediately prior to randomization. Randomization lists used for preparation of envelopes will be stratified by site and will use the block urn design [17] to minimize imbalance while also ensuring the sequence is not predictable based on previous assignments. The block urn design is suitable for unequal allocation ratios when there are more than two arms.
As of the beginning of the screening process (day -08 up to day -01) until discharge (on day 15), patients will be hospitalized to ensure adherence to the screening- and protocol-procedures.
After completion of the course of study drugs (on day 14), all patients will be referred to a governmental clinic to complete the TB treatment, according to national governmental standards to complete 6 months of first line treatment.

An interim analysis in Stage 2 will be conducted after 5 patients per BTZ-043 receiving arm 1-3 complete treatment. The analysis will evaluate the bactericidal activity, PK, and PK-PD relationship of the different doses of BTZ-043, given daily over 14 days.
After this interim analysis in Stage 2, the TSC will decide whether to add two potential additional arms.
When the TSC supports the decision for 2 additional arms of BTZ-043, these arm 5 and 6 patients will be recruited through random allocation after arm 1-4 are fully enrolled.

Expected trial duration per participant is 23 days (±2 days) from enrolment on day 0, followed by a treatment period of 14 days, discharge at day 15 up to and including a follow-up period of seven days (±2 days).

5.2 Measures to prevent Bias

This study will be conducted with patients and physicians being aware of treatment allocation. To ensure unbiased assessment of endpoints, the personnel assessing patients' outcomes, like the microbiology and safety laboratory staff, will remain blinded to treatment assignment throughout the whole study. Every effort will be made to maintain this blinding.
Further, there will not be any cumulative summary of study data by randomized treatment arms generated, with the exception of stage 1 data to be provided to the TSC for dose escalation meetings, or ad-hoc stage 2 meetings triggered by safety events, by the unblinded statistician. Such analysis may not be distributed outside of the TSC.
Determination of MICs for the experimental treatment allocated to the patients will only be made after all other assessments of patient samples have been completed in the respective laboratory or will be done at a different specialised laboratory.

5.3 Trial Endpoints

Patients will be regularly assessed for adverse events (AEs), including vital signs, pre-dose physical examinations, weight, neurological examinations, vision testing, 12-lead ECG, routine clinical laboratory tests (including chemistry, haematology)

5.3.1 Primary Endpoint

Safety and tolerability of BTZ-043: any occurence of AEs during treatment and follow-up phase, including

- changes in clinical observations from baseline
- changes in vital signs from baseline
- changes in serum chemistry, haematology and coagulation from baseline measurements
- changes in ECG, incl. heart rate, PR interval, QRS, QT interval, QTcF, morphological abnormalities, from baseline

5.3.2 Secondary Endpoints

1. <u>Secondary Bactericidal Activity Endpoints:</u>
   The bactericidal activity of different doses and, if the additional arms are added, of single daily dosing vs. split dose of the BTZ-043 will be evaluated by measuring the rate of change in sputum viable bacterial load between day -1 and day 15 by a change in the following endpoints that describe bacterial load per sample:
   - changes in time to detection in the BD MGIT™ liquid media culture system from baseline
   - changes in solid media colony forming units (CFU) from baseline
   - changes in sputum LAM (experimental endpoint) and sputum MBLA (experimental endpoint) from baseline

2. <u>Secondary Pharmacokinetic Endpoints:</u>
   a) PK of BTZ-043 and its major metabolites BTZ-045S and M2 and other metabolites of interest after a single dose and at steady state as
      - area under the plasma concentration curve from dosing to the end of the dosing interval (AUC0-24) and to infinite (AUC0-inf)
      - observed maximum concentration (C_{max})
      - time to reach C_{max} (T_{max})
      - minimum observed plasma concentration 24 hours following the last dose (C_{min})
      - Clearance (Cl)

- Volume of distribution (Vd)
- Elimination half-life ($T1_{/2}$)
- Relation of efficacy measurements (pharmacodynamics) to pharmacokinetic indices of BTZ-043 and its metabolites (AUC, C_{max})

b) Inter-individual differences of PKs of BTZ-043 and its metabolites between day 1 and day 14

c) Changes in PKs of BTZ-043 after a high fat high calorie meal in comparison to the PK under fasting conditions during the 1st stage.

d) Changes in PKs of the probe drugs administered on day 0 and day 14 during the 2nd stage.

e) Changes in plasma concentrations, amount excreted into the urine and renal clearence values of appropriate biomarker(s) measured in plasma and/or urine on blood/urine sampling days.

5.4 Study Population and Eligibility Criteria

A total of up to 105 (see section 7.4) male and female patients, aged ≥ 18 – 64 years, with newly diagnosed, smear positive, drug sensitive pulmonary tuberculosis will be enrolled in 2 stages.
In case of a high number of dropouts or non-evaluable patients, it may be necessary to recruit more participants into the study (see Sample size determination, page 86).

5.4.1 Inclusion Criteria

Participants are required to meet **all** of the following criteria in order to be included in the trial:

<u>General inclusion criteria:</u>

1. Provide written, informed consent prior to all trial-related procedures including HIV testing.
2. Understand and willing to comply with the study procedures.
3. Male or female adults aged 18 up to and including 64 years.
4. Body weight (in light clothing and with no shoes) ≥ 40 kg.
5. Participants are either unable to conceive/father children AND/OR they will be using effective methods of contraception, as defined below:

   Non-childbearing condition:

   - Female participant/sexual partner of male participant: bilateral oophorectomy and/or hysterectomy or bilateral tubal ligation ≥ 12 months ago and/or has been postmenopausal with a history of no menses for ≥ 12 consecutive months as per medical history

- Male participant/sexual partner of female participant: vasectomised and/or bilateral orchiectomy ≥ 3 months prior to screening as per medial history
- Female pregnant sexual partner of male participant: agree to use protective method specified below
- Male sexual partner of male participant: agree to use protective method specified below
- Abstaining from sexual intercourse, but agreeing to use effective methods of contraception/protection as described below, should this situation change

Effective contraception methods:

- Female participants: two methods, including methods used by the patient's sexual partner(s). At least one to be a barrier method. Contraception must be practised for at least until 12 weeks after the last dose of BTZ-043.
  (Note: hormone-based contraception alone may not be reliable when taking RIF during continuation Phase; therefore, hormone-based contraceptives alone cannot be used by female participants/female partners of male participants to prevent pregnancy).
- Male participants: must ensure effective contraception (two methods) for at least 12 weeks after the last dose of BTZ-043, including at least one barrier method.

Effective protective methods:

- Male participants with female pregnant sexual partner: are required to use at least one barrier method for at least until 12 weeks after the last dose of BTZ-043 for protection of the pregnant partner and the pregnancy.
- Male participants with male sexual partner: are required to use at least one barrier method for at least until 12 weeks after the last dose of BTZ-043 for protection of the partner.

<u>Disease-specific inclusion criteria:</u>

6. Newly diagnosed, previously untreated current episode of drug-susceptible pulmonary TB (presence of MTB complex with rapid molecular test result confirming susceptibility to RIF and INH such as "GeneXpert" and/or "HAIN MTBDR plus")
7. Chest X-ray (no older than 2 weeks) which, in the opinion of the Investigator, is consistent with TB
8. Ability to produce an adequate volume of sputum (approximately 10ml estimated overnight production)

9. ≥ 1 sputum sample from concentrated sputum positive for acid-fast bacilli on microscopy (at least 1+ on the IUATLD/WHO scale) from either a spot sputum or overnight sputum sample.

5.4.2 Exclusion Criteria

Participants for whom **one** of the following criteria is met will be excluded from participating in the trial:

General exclusion criteria:

1. Poor general condition, where delay in treatment cannot be tolerated or death within three months is likely, as assessed by the investigator.
2. The patient is pregnant or breast-feeding.

Disease-specific exclusion criteria:

3. The patient is infected with HIV.
4. The patient has a known intolerance to any of the study drugs or concomitant disorders or conditions for which study drugs or standard TB treatment are contraindicated.
5. Treatment with any other investigational drug within 1 month prior to enrolment or enrolment into other clinical (intervention) trials during participation.
6. The patient has a history of or current evidence of clinically relevant cardiovascular, metabolic, gastrointestinal, neurological, ophthalmological, psychiatric or endocrine diseases, malignancy or any other condition, that will influence treatment response, study adherence or survival in the judgement of the investigator, especially:
   a. Clinically significant evidence of severe TB (e.g. miliary TB, TB meningitis, excluding limited lymph node involvement)
   b. Serious lung conditions other than TB or significant respiratory impairment in the discretion of the investigator
   c. Neuropathy, epilepsy or significant psychiatric disorder
   d. Any diabetes mellitus
   e. Cardiovascular disease, such as myocardial infarction, heart failure, coronary heart disease, arrhythmia, tachyarrhythmia, or pulmonary hypertension
   f. Current (as measured on two occasions during screening) or history of hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg) AND/OR ever received antihypertensive treatment
   g. Long QT syndrome or family history of long QT syndrome or sudden death of unknown or cardiac-related cause
   h. Alcohol or other drug abuse, that is sufficient to significantly compromise the safety or cooperation of the patient, includes substances prohibited by

the protocol, or has led to significant organ damage, at the discretion of the investigator

i. Condition that makes ophthalmologic assessment difficult or render results unreliable

Laboratory exclusion criteria at screening:

7. Serum amino aspartate transferase (AST) and/or alanine aminotransferase (ALT) activity >2.5x the ULN
8. serum alkaline phosphatase (ALP)> 2.5x the ULN
9. serum total bilirubin level >1.5 times the ULN
10. estimated creatinine clearance (eCrCl) using the Cockcroft and Gault formula level lower than 60 mls/min
11. haemoglobin level <8.0 g/dL
12. platelet count <100,000/mm3
13. serum potassium below the lower level of normal (LLN) for the laboratory

ECG-specific exclusion criteria:

14. QTcF of > 450 milliseconds (ms)
15. Atrioventricular (AV) block with PR interval > 200 ms
16. QRS complex > 120 ms
17. any other changes in the ECG that are clinically relevant as per discretion of the investigator

Restricted medication:

18. Treatment with drugs active against MTB within the last 3 months prior to screening
19. Requires medication as included in the following drug classes within 2 weeks prior to the first dose of study treatment:
    - medication that prolongs the QTc interval
    - CYP 450 inhibitors or inducers, including grapefruit containing foods / beverages and St. John's Wort
20. Requires medication as included in the following drug class within 2 days prior to the first dose of study treatment
    - antacids or antipeptic drugs (antacids, H2 blockers, proton pump inhibitors)

5.5 Schedule of Events

The trial consists of the following periods and timepoints:

- Screening: Visit 1 - Screening Visit (Day –8 to -1)
- Enrolment: Visit 2 - Baseline/Inclusion Visit (Day 0)
- Treatment: Visit 3 – Visit 16 (Day 1 - 14)

- Discharge: Visit 17 (Day 15)
- Follow-up: Visit 18 (Day 22 ± 3)

A tabular overview of the individual timing and details of the respective procedures and laboratory samples to be done at each visit can be found in the schedule of events table.
Should this be required for practical reasons by a site, assessments related to screening and enrolment visit can be performed additionally at more than these visits.

5.5.1 Screening Period

Visit 1 (day -8 to -1)		
Administrative & regulatory		• Written informed consent • Assign participant number • Hospitalization
Clinical		• Demographic data: Date of birth, ethnic group, sex • Medical history, incl. treatment history and current concomitant medication • Physical examination, including respiratory, cardiovascular and other organ systems • Vital signs (temperature, blood pressure, pulse) after 10 mins supine rest • Weight (kg)/height (m) • Neurological examination (including cranial nerves, biceps, patellar, Achilles tendon reflex, equilibrium, gait, cognition (time and localisation) • Ophthalmological Assessment
Laboratory	Blood	• Serum pregnancy test, if female of childbearing potential • Serology (HIV, HCAb, HBsAg) • Screening laboratory • Pharmacogenomic blood sample, if consent given on a separate form

<u>Urine</u>	• Urine drug screening • Urinalysis
Sputum	• Spot sputum or overnight sputum (smear from concentrated sample for acid-fast bacilli) • Susceptibility testing for RIF and INH by rapid test • Minimum inhibitory concentration (MIC) for BTZ-043 • Overnight sputum collection for – Volume – smear from concentrated sample for acid-fast bacilli, if spot sputum has not been collected – Susceptibility testing for RIF and INH by rapid test, if spot sputum has not been collected – bacterial load (time to detection in the BD MGIT™ liquid media culture system) – Microbiological analysis of colony forming units (CFU) on solid media – Quantification of LAM measured by Elisa – MBLA, an assay to measure mycobacterial load by quantifying 16S rRNA from sputum samples
Other	• Inclusion and exclusion criteria • Chest X-ray (if no chest X-ray is available no older than 2 weeks) • ECG (12-lead, single) after 10 mins supine rest
Study drugs	• N/A

5.5.2 Enrolment Period

<u>Visit 2 (day 0)</u>	
Administrative & regulatory	• Complete final check of in-/exclusion criteria • Before or at this visit: randomization to arm, and if randomized to BTZ-043 arm 1-3, further randomization to probe drug cocktail vs. dolutegravir*
Clinical	• Concomitant medication • Adverse events

		• Vital signs (temperature, blood pressure, pulse and respiratory rate) to be recorded after at least 10 min supine rest
Laboratory	Blood	• Intensive PK sampling for probe drugs**. If deemed necessary by the investigator, this may be moved to day -1.
	Urine	• optional: 24 urine collection on Day 0 **
Sputum		• Overnight sputum collection** for assessment of – Volume – bacterial load (time to detection in the BD MGIT™ liquid media culture system) – Microbiological analysis of colony forming units (CFU) on solid media – Quantification of LAM by Elisa to investigate the bacterial load per sample – MBLA, an assay to measure mycobacterial load by quantifying 16S rRNA from sputum samples
Study drugs		• Probe drug administration**. If deemed necessary by the investigator, this may be moved to day -1, along with the intensive PK sampling for probe drugs.

**Applies to Stage II only, can be done at this or earlier visits*

*** Applies to participants in Stage 2 in BTZ-043 arms 1-3 only*

5.5.3 Treatment Period

Visits 3 – 16 (day 01 - day 14)	
Administrative & regulatory	• Hospitalization (Day 1 - 14)
Clinical	• Complete physical examination, including neurology on Day 14 • Symptom related physical examination (Day 1 – 13) • Vital signs (temperature, blood pressure, pulse and respiratory rate) to be recorded after at least 10 min supine rest. Temperature recorded once, blood pressure and pulse recorded within 2 hours before dosing, 1h ± 15min, 2h ± 15 min, 8h ± 15 min after dosing.

		• triplicate 12-lead ECG(Day 1, 7 and 14) to be collected ≥ 1 to ≤ 5 min apart; within 2 hours before dosing, 1h ± 15min, 2h ± 15 min, 8h ± 15 min after dosing • Concomitant medication • Adverse events
Laboratory	Blood	• Safety Lab (Day 2, 4, 7, 10, 14) *(Coagulation only on Day 2, 7, 14 or if clinically indicated);* to be sampled before study treatment administration • Serum pregnancy test, if female of childbearing potential (Day 14) • Intensive PK sampling for BTZ-043 – stage 1: Days 1, 12, after high-caloric breakfast: day 14** Stage 2: days 1, 14 • Intensive PK sampling for probe drugs (Day 14)*
	Urine	• Urinalysis (Day 2, 4, 7, 10, 14) • Optional: 24h urine collection on day 14*
Microbiology		• Overnight sputum collection (Day 2, 3, 4, 6, 8, 11, 14) for – Volume – bacterial load (time to detection in the BD MGIT™ liquid media culture system) – Microbiological analysis of colony forming units (CFU) on solid media – Minimum inhibitory concentration (MIC) for BTZ-043 (day 14 only, or other isolate obtained earlier, if day 14 cultures are negative) – Quantification of LAM by Elisa to investigate the bacterial load per sample – MBLA, an assay to measure mycobacterial load by quantifying 16S rRNA from sputum samples
Other		• Stage 1: high-caloric breakfast before administration of BTZ-043 (Day 14)**
Study drugs		• drug dispensing, intake of day's dose • Stage 2: probe drug administration (Day 14)* • Compliance assessment

** Applies to participants in Stage 2 in Arms 1-3 receiving BTZ-043 only*
***Applies to Stage I only*

5.5.4 Discharge Period

Visit 17 (day 15)		
Administrative & regulatory		• Hospitalization and discharge after last assessments
Clinical		• Vital Signs • Symptom related physical examination • Concomitant medication • Adverse events • Ophthalmological Assessment (may be moved to day 13, 14, or the next working day to come)
Laboratory	**Blood**	• N/A
	Urine	• N/A
Microbiology		• N/A
Other		• N/A
Study drugs		• N/A (Patients are to be started on their first-line treatment for TB either at this visit or at their government health clinic, at the discretion of the investigator)

5.5.5 Follow-up Period

Visit 18 (day 22 +/- 3 days)	
Administrative & regulatory	• N/A
Clinical	• Vital Signs • Symptom related physical examination • Adverse events • Follow-up of Adverse Events, including ophthalmological examination, if required

Laboratory	**Blood**	• Follow-up of clinically significant abnormal blood results
	Urine	• N/A
Microbiology		• N/A
Other		• N/A
Study drugs		• N/A

The follow-up visit at Day 22 (+/-3 days) should generally be performed by a personal visit as per SOE, if the current situation in the country allows.
During the COVID-19 pandemic, it is mandatory to minimize the risk for study personnel and participants, so as per investigators discretion this visit may be performed by phone, while the COVID-19 pandemic is ongoing, unless there is need to follow up on new complaints since the last visit, reported by the patient, abnormal blood results, clinical assessments or new and ongoing AE's, that need to be followed-up by physical contact. In case a face-to-face visit has to be performed, the safety measures implemented by the study sites need to be followed strictly.

5.6 Sub-studies

This study provides the opportunity to advance the scientific understanding of TB disease and treatment, within a well-controlled clinical trial generating valuable data on treatment response in a large cohort of participants, with GCP-related quality control and assurance producing high data quality.
It is therefore ethically mandated to use this opportunity to advance the science around TB and TB treatment by making use of this resource, in order to accelerate future developments to the benefit of TB patients and persons at risk of TB diseases.
During this trial, samples collected and stored might be subject to further investigations. Further assessments of these samples will only be done if the site's ethics committee has accepted the conduct of these sub-studies, and if a study participant provides separate consent, on forms separate from consent for the main trial. Study participants will be able to refuse retention sample collection while still participating in the main trial.
Sample(s) will be kept until they are all used up or destroyed at the Sponsor' s discretion, which may take up to fifteen years, with extension if needed. If the specimens are going to be stored for longer, we will ask permission from the local ethics committee.
The use of these samples will be decided on by the PanACEA executive group, upon applications of individual researchers or teams for use of trial samples. Results of these

analyses will not be incorporated into the trial reports, and will not be disclosed to investigators before the completion of the trial.
Retention samples will be whole blood for pharmacogenomic analyses if separate consent to such is given. Pharmacogenomic analysis may include sequencing of genes related to the uptake, metabolism and excretion of BTZ-043; such genes may include those coding for hepatic CYP enzymes, pregnane X-receptor or other genes related to hepatic enzyme induction, UGT – transferases etc.
Serum, sputum and urine samples may be analysed for potential correlates of treatment success and bacterial load, using antigen – based, PCR-based, other microbiological or imaging tests.
Storage and analyses of these samples may be performed outside of the countries hosting the trial site(s). The possibility of sample transport and analyses abroad will be included into the informed consent form provided to the patient before consenting.
All use of stored samples, which is not identical with intentions and/or methods described in this protocol, shall be submitted to the relevant IRBs before any sample is used.

6. Trial Assessments

6.1 Demographic and Background Assessments

Following demographic and background variables will be collected according to the schedule of events table:

- Written informed consent
- Inclusion and exclusion criteria
- Demographic data: date of birth, ethnic group (e.g. African, Asian, Caucasian etc.), sex (f/m)
- Weight in kilograms (kg)
- Height in meters (m)
- Clinically significant medical and treatment history
- Birth control method (for female and male subjects)
- Concomitant medications (prescription medications, over-the-counter (OTC) medications, herbal/traditional medical formulations) until 14 days prior to enrolment
- Alcohol, caffeine, nicotine, drug intake and until 14 days prior enrolment
- Chest X-ray (X-ray images performed at non-study facilities may be accepted if there is reasonable certainty that the patient' s ID is correct, and if they are not older than 2 weeks)

6.2 Safety Assessments

The following safety variables will be assessed for evaluation of safety endpoints according to the schedule of events table.

6.2.1 Physical Examination and Vital signs

The investigator will conduct a complete pre-dose physical examination, any significant findings will be recorded in the eCRF, including findings caused by the disease under study.

- Systolic and diastolic blood pressure (BP, mmHg) and heart rate (bpm) to be measured supine (after 10 minutes of rest, within 2 hours before dosing and at 1h (± 15 min), 2h (± 15 min) and 8h (± 15 min) post drug-administration) using a standard cuff and using the same type of sphygmomanometer or device, if possible by the same observer, at each visit. Should the BP values mentioned in the exclusion criteria be exceeded, a re-measurement may be done after another appropriate period of rest (around 10-15 minutes), as anxiety is expected to increase BP during the participant's first study visit.
- Body temperature (°C)
- Weight (kg) will be recorded in light clothing without shoes. Sites should minimize inter instrument variation by measuring an individual patient's weight on the same, calibrated instrument throughout the entire study.
- Height (m) (at screening only)
- Neurological Examination, incl. cranial nerves, biceps, patellar, achilles tendon reflex, equilibrium, gait, cognition (time and localisation)

Ophthalmological examination, incl. history of eye diseases, visual acuity and refractive errors (Snellen Chart), colour vision testing (Ishihara), examination of the pupils, ocular motility and alignment, intraocular pressure, external examination of the eye, slit-lamp examination, fundoscopic examination, optical coherence tomography (OCT).

6.2.2 Safety Laboratory

The laboratory samples are to be collected prior to dosing and after recording pre-dose vital signs and a 12-lead ECG (if ECG is done on the respective visit). A more detailed description of sample collection, processing, storage and shipment will be provided in the Laboratory Manual.

- Haematology*: full blood count, haemoglobin, haematocrit, red blood cell count, white blood cell count with differential, platelet count
- Serum Chemistry*: Glucose, Uric Acid, Urea, electrolytes (Sodium (Na^+), Potassium (K^+), Total Serum Calcium (Ca^{2+}), Magnesium (Mg^{2+}), Chloride (Cl^-), Phosphate (PO_4^{3-})), total Protein, total direct and indirect (calculated) Bilirubin, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (AP), Gamma-glutamyl

Transferase (GGT), Serum Creatinine, estimated glomerular filtration rate (eGFR), low density lipoprotein (LDL)

- Coagulation: activated partial Thromboplastin time (APTT), Prothrombin time (PT), international normalized ratio (INR) for PT
- Dipstick Urinalysis*: glucose, protein, leucocytes, erythrocytes, protein, pH, urobilinogen; Urine microscopy to follow up on abnormal dipstick results as per the investigator's decision
- Urine Drug Screening (screening visit only): Testing for opiates, amphetamines, cannabis, cocaine, benzodiazepines and barbiturates. Should a test kit be used that generates additional variables, these will be reviewed and considered by the investigator for a decision on including the participant.
- Serum pregnancy test: if female of childbearing potential (Screening and Visit 16)
- Serology: HIV, Hepatitis C Antibodies (HCAb), Hepatitis B surface Antigen (HBsAg)
- Additional investigations will be ordered by the investigator, if they are in the subject`s best interest. Any laboratory tests needed for emergency safety assessment can be sent to the nearest local laboratory as per discretion of the investigator.

*performed during safety laboratory assessment, complete package done during screening only

6.2.3 Chest Radiography (X-ray)

An erect posterior-anterior (PA) chest X-ray will be performed at screening, if no chest X-ray is available no older than 2 weeks.

6.2.4 ECG

At screening, a single ECG is sufficient.
During treatment phase, triplicate ECGs will be recorded within 2 hours before dosing and at 1h (± 15 min), 2h (± 15 min), and 8h (± 15 min) post drug-administration. Triplicate ECGs should be collected ≥ 1 to ≤ 5 minutes apart. The following ECG variables will be assessed: Heart rate, PQ interval, QRS, QT and QT corrected for heart rate using Friderica's correction (QTcF), morphological abnormalities.

- Single 12-lead ECGs will be recorded pre-dose for at least 10 seconds, at 50mm/second or greater
- Timing and recording technique for ECGs will be standardized for all participants. Patients should be lying down (recumbent) for at least 5 minutes prior to each 12-lead ECG evaluation.
- For each participant, the ECG should be collected at around the same time of day, within 2 hours before dosing.

- ECGs will be analysed centrally by sponsor-appointed specialist physician(s).

Due to delays inherent in the centralized analysis procedure, the investigator will make an immediate preliminary analysis of the ECG tracings recorded during the visits in the treatment phase. Should the investigator decide that an ECG is of insufficient technical quality, the procedure is to be repeated. Preliminary analysis will be done especially with regard to technical quality of the ECG, abnormalities concerning the patient's safety, namely morphological abnormalities, arrhythmias of concern (e.g. grade III AV block, ventricular arrhythmias exceeding single extra systoles) and the QTc stopping criteria of a prolongation of QTcF of >500ms in total.

The investigator will note whether an ECG stopping criterion has been met, sign and date the ECG printout during the patient's visit in order to confirm preliminary ECG review.

Only data from sponsor-appointed ECG specialist review will be used for eligibility assessment during screening and entered into the study database. Data from the preliminary site investigator review will not be used for this purpose.

6.3 Pharmacokinetic Assessment

6.3.1. Pharmacokinetic blood sampling

All participants in stage 1 will undergo intensive PK sampling during visit 3, 14 and 16 (Days 1, 12 and 14). Participants in BTZ-043 arms of the 2nd stage of the trial will undergo intensive PK sampling during visit 2 (BTZ arms 1-3 only), 3 and 16 (Day 0 (BTZ arms 1-3 only), 1, 14).
If deemed necessary by the investigator, the day 0 intensive PK sampling, and corresponding probe drug administration, may be moved to day -1.
Time points for blood samples will be at 0.0h (pre-dose) and post-dose at 15min, 30min, 1.0h, 1.5h, 2.0h, 3.0h, 4.0h, 6.0h, 8.0h, 10.0h, 12.0h, 24.0h (pre-dose the following day). Time window: 0h – 2h (± 5 min), 3h – 24h (± 10 min)

Times of IMP and probe drug administration and times of sampling will be recorded in the eCRF.

Further description will be provided in a laboratory manual, to be provided to the sites before study start. Testing will be performed by the appointed pharmacokinetic laboratory.

The volume of the blood samples per time point is limited. In case, after sample work-up, the amount of available plasma is too low to comply with the amounts required by the PK-Lab Manual for BTZ-043 analysis, the aliquots with stabilizer shall be filled first. Then the first aliquot without stabilizer shall be filled with the required amount. The remainder goes to the second non-stabilized aliquot.

It is crucial, that one stabilized sample and the first non-stabilized sample containing the correct amount of plasma are shipped to the PK lab. The remaining aliquots will be stored on-site as back-up samples.

6.3.2. Pharmacokinetic 24h urine sampling

In stage 2, the sponsor may decide to conduct 24h – urine sampling if results from the BTZ-043 preclinical development programme suggest that measurement of endogenous biomarkers for transporter activity would be worthwhile.

For this, patients will be asked to void their urine into a collection container for 24h. This collection container will be kept refrigerated at 4°C during collection. After the collecting time is completed, the content will be mixed and an aliquot of 10ml will be stored frozen at -80°C.

6.4 Efficacy Assessment

The methodology for the following assessments will be described in detail in the Laboratory Manual, which will be supplied to the trial sites before study start. The following efficacy variables will be assessed for evaluation of efficacy endpoints, at the time points indicated in the Schedule of Events.

6.4.1 Spot Sputum

Participants will be shown images of what good quality sputum samples should look like, which reportedly has led to better sample quality and higher detection rates of MTB.
Before producing a sample, participants should first rinse their mouth with clean water, then they should deeply inhale three times and cough deeply to produce a good quality sample, trying to avoid saliva and nasal secretions. The spot sputum sample collected at Screening will be collected for acid-fast bacilli (smear from concentrated sample) and susceptibility testing for RIF and INH by rapid test; multiple spot sputum samples might be collected for assessments of smears and molecular resistances. Those tests may be done from overnight sputum samples as well.

6.4.2 Overnight Sputum Collection

Patients will be asked to collect overnight sputum at Screening and on days 0, 2, 3, 4, 6, 8, 11, 14. They will be instructed to do so according to the Laboratory Manual.
The following assessments will be carried out from overnight sputum:

- Volume
- Bacterial load (time to detection of TB bacteria in BD MGIT™ liquid media culture system)
- Microbiological analysis of colony forming units (CFU) on solid media
- Quantification of LAM by Elisa to investigate the bacterial load per sample
- MBLA, an assay to measure mycobacterial load by quantifying 16S rRNA from sputum samples

Overnight samples during screening may as well be used for smear and susceptibility testing to RIF and INH (such as “GeneXpert” and/or “HAIN MTBDR plus”).

7. Study Treatments

7.1 Study Drug Description

The following medication will be used in the study according to Schedule of Events, page 16:

BTZ-043:

BTZ-043 is a drug under development and not approved yet. It will be manufactured and analysed according to Good Manufacturing Practice (GMP) requirements. The Sponsor will provide the Regulatory Authorities and the Ethical Review Boards with a GMP certificate of the manufacturer of the BTZ-043 tablets; Certificates of Analysis (CoA) of the batches to be used and an Investigational Brochure (IB) that summarizes Chemistry Manufacturing and Control (CMC) preclinical and clinical data with respect to BTZ-043.
Patients in stage 1 will receive BTZ-043 orally once daily in different doses according to dose escalation scheme:

- Cohort 1 (BTZ250): patients will receive 250 mg of BTZ-043
- Cohort 2 (BTZ500): patients will receive 500 mg of BTZ-043
- Cohort 3 (BTZ750): patients will receive 750 mg of BTZ-043
- Cohort 4 (BTZ1000): patients will receive 1000 mg of BTZ-043
- Cohort 5 (BTZ1250): patients will receive 1250 mg of BTZ-043
- Cohort 6 (BTZ1500): patients will receive 1500mg of BTZ-043
- Cohort 7 (BTZ1750): patients will receive 1750mg of BTZ-043
- Cohort 8 (BTZ2000): patients will receive 2000mg of BTZ-043

The TSC may decide to stop escalation or recruit more than three participants to each dose cohort.

Patients in stage 2 will receive BTZ-043 orally once daily in the experimental arms in 3 different doses:

- Arm 1 (BTZ_{high}) with a higher dosage of BTZ-043, proven to be safe in 1st stage (1000mg)
- Arm 2 (BTZ_{med}) with a medium dosage of BTZ-043, proven to be safe in 1st stage (500mg)
- Arm 3 (BTZ_{low}) with a lower dosage of BTZ-043 proven to be safe in 1st stage (250mg)

The TSC may decide to add up to two additional arms of BTZ-043 with a dosage to be determined after an interim analysis after 5 patients per BTZ-043 receiving arm 1-3 complete treatment. Patients in these arms (arm 5 and arm 6) will receive a dose in the range proven safe in stage 1 (250mg – 1750mg). These doses may be given as a once-daily administration or split-dose administration (twice daily), and the new arms may differ in once-daily vs. split dosing.

Rifafour e-275® (or equivalent).:

Each tablet Rifafour e-275® contains INH, RIF, Pyrazinamide and Ethambutol as:

- Rifampicin 150 mg
- Isoniazid 75 mg
- Pyrazinamide 400 mg
- Ethambutol 275 mg

RIF, INH, Pyrazinamide and Ethambutol are approved drugs for single as well as for use in this fix combination. Patients in the control group will be treated for their TB with this 4 drug fixed combination therapy according to South African National Guidelines. Product Information Leaflets for the TB drug fixed-dose combinations with these drugs will be provided to investigators.

During the 2nd stage patients in the control arm (Arm 4 (control)) will receive a standard dose of Rifafour e-275® orally once daily adapted to body weight (38-54,9 kg: 3 tablets; 55 – 70,9 kg: 4 tablets; > 70 kg: 5 tablets). For determination of doses, weights are to be rounded off to the nearest integer.

The product Information Leaflet for Rifafour e-275®: is included in Appendix 8.

Probe Drug Cocktail:

Phenotyping for drug metabolizing enzymes or transporters is defined as measuring its actual in vivo activity in an individual [7]. This is performed by single administration of a selective substrate for this enzyme (‘probe’ drug) and subsequent determination of a phenotyping ‘metric’. The metrics used may be pharmacokinetic measures such as exposures, clearance, or absorption rate in the case of a transporter. Other parameters such as single point probe concentrations or ratios of metabolite over parent concentrations in plasma, saliva and/or urine are also often used.

Instead of administering one probe drug, multiple probe drugs can be applied simultaneously to assess the activity of various metabolic enzymes and transporters at the same time. This ‘cocktail’ approach is cost-effective and it is also advantageous from an ethical point of view to include a much lower number of individuals in clinical studies to resolve a question. Of course, it must be excluded that the various substrates cause mutual pharmacokinetic drug–drug interactions and this must be validated. In addition, the probe drugs should not have

pharmacodynamic interactions (i.e. the same adverse effect), but this can be prevented by using low doses.
In this study we will administer the validated Cologne cocktail, without omeprazole probe drug for CYP2c19), as we considered that its effect on the pH of the stomach may possibly affect BTZ-043 bioavailability. The Cologne cocktail is a state-of-the-art phenotyping cocktail for assessing the drug-drug-interaction (DDI) potential of test drugs. The probe drugs are specific for individual CYPs, there are no interactions between these probe drugs, and they are among those that may be considered best validated.

The following drugs will be given to 2/3 of the randomized patients in the BTZ-043 intervention arms 1-3 during stage 2 after inclusion on da
y 0 and on day 14:

- Caffeine: 1 tablet à 150mg (≡ 150mg)
- Tolbutamide: 1/4 tablet à 500mg (≡ 125 mg)
- Digoxin: 2 tablets à 0.25mg (≡ 0.5mg)
- Dextromethorphan: 10mL syrup à 15mg/5mL (≡ 30 mg)
- Midazolam: 2mL solution à 5mg/5mL p.o. (≡ 2mg)

All of the drugs given within the probe drug cocktail are approved for use in adults. Product Information Leaflets for the TB drug fixed-dose combinations with these drugs will be provided to investigators.

The following drug will be given to 1/3 of the randomized patients in the BTZ-043 intervention arms 1-3 during stage 2 after inclusion on day 0 and on day 14

<u>Dolutegravir:</u>
Dolutegravir is a HIV-1 integrase strand transfer inhibitor (INSTI), which is FDA approved. Patients in stage 2 will be randomized to receive 1 tablet à 50mg p.o. once on day 0 and on day 14. Product Information Leaflets for the TB drug fixed-dose combinations with these drugs will be provided to investigators.

7.2 Study Drug Dosage and Administration

The experimental and control treatment as described above will be administered for 14 days according to the following table.
Patients receiving the investigational drug in cohorts 1 – during stage 1 will take BTZ-043 in fasting state on Day 1-13. Patients are allowed to have breakfast **1 hour after** the daily dose of BTZ-043 has been taken.

On Day 14 during stage 1 a high-caloric breakfast should be consumed **within 20-30 min** (start until end of breakfast). Dosing of BTZ-043 on Day 14 will take place **within 30 min after the breakfast has been entirely consumed**. The breakfast should contain the following calories, half of which should be provided in fat (according to the following recommendation from the U.S Department of health and Human Services, Food and Drug Administration Centre for Drug Evaluation and Research (CDER) [18]:

Meal Type	Total Kcal	Fat		
		Kcal	Grams	Percent
High-Fat	800-1000	500-600	55-65	50

Calories From Protein	150
Calories from Carbohydrates	250

In this trial, patients will receive a standardised high-fat breakfast 30 min pre-dosing on Day 14 during stage 1, consisting of **all** of the following or similar ingredients*:

- 200 mL tetra pack 100% orange juice
- 2 slices brown bread
- 10 d (2 Teaspoons) margarine
- 1 slice Cheddar sliced cheese (or lactose-free Cheddar for lactose-intolerant participants)
- 100 g scrambled eggs
- 100 g Boerewors
- 100 g Tomato and Onion Smoor

**Provides 954 Kcal: 536 Kcal from Fat (60g), 148 Kcal from Protein (37g), 270 from Carbohydrates (68g)*

In stage 2, study drug will be taken together with a breakfast that will be more aligned with TB patients' eating habits in South Africa. The breakfast is composed to contain around 500-600 kcal and around 25-35% calories from fat.
Breakfast will be consumed immediately after the intake of IMP-study drug. The IMP-study drug has to always be administered at the same time.

In case of a split-dose administration in the additional BTZ arms, a predefined meal to be taken immediately after the intake of the study drug, will be provided for the evening dose. Probe drug cocktail or dolutegravir, as specified under 7.1., will be taken 2 hours before the breakfast is served to the participant (arms 1-3 only).

The comparator treatment will have to be taken on an empty stomach at all times.

Table 3. Daily Dosing of Study Drugs

Stage 1	**BTZ-043 250 mg tablet**
Cohort 1 (BTZ_{250})	*Day 01-14:* 1 tablet to be taken orally once per day in the mornings
Cohort 2 (BTZ_{500})	*Day 01-14:* 2 tablets to be taken orally once per day in the mornings
Cohort 3 (BTZ_{750})	*Day 01-14:* 3 tablets to be taken orally once per day in the mornings
Cohort 4 (BTZ_{1000})	*Day 01-14:* 4 tablets to be taken orally once per day in the mornings
Cohort 5 (BTZ_{1250})	*Day 01-14:* 5 tablets to be taken orally once per day in the mornings
Cohort 6 (BTZ_{1500})	*Day 01-14:* 6 tablets to be taken orally once per day in the mornings
Cohort 7 (BTZ_{1750})	*Day 01-14:* 7 tablets to be taken orally once per day in the mornings
Cohort 8 (BTZ_{2000})	*Day 01-14:* 8 tablets to be taken orally once per day in the mornings

Stage 2	**BTZ-043 250 mg tablet**	**Rifafoure-275® tablet *******	**Caffeine 150mg tablet ******	**Tolbutamide 500 mg tablet ******	**Digoxin 0.25mg tablet ******	**Dextromethorphan: 15mg/5mL syrup ******	**Midazolam 5mg/5mL solution ******	**Dolutegravir 50mg tablet*****
Arm 1 (BTZ_{1000mg})	*Day 01-14:* 4 tablets to be taken orally once per day in the mornings*		*Day 00 and 14:* 1 tablet to be taken orally once per day in the mornings	*Day 00 and 14:* 1/4 tablet to be taken orally once per day in the mornings	*Day 00 and 14:* 2 tablets to be taken orally once per day in the mornings	*Day 00 and 14:* 10 mL solution to be taken orally once per day in the mornings	*Day 00 and 14:* 2 mL solution to be taken orally once per day in the mornings	*Day 00 and 14:* 1 tablet to be taken orally once per day in the mornings
Arm 2 (BTZ_{500mg})	*Day 01-14:* Respective 2 tablets to be taken orally once per day in the mornings*		*Day 00 and 14:* 1 tablet to be taken orally once per day in the mornings	*Day 00 and 14:* 1/4 tablet to be taken orally once per day in the mornings	*Day 00 and 14:* 2 tablets to be taken orally once per day in the mornings	*Day 00 and 14:* 10 mL solution to be taken orally once per day in the mornings	*Day 00 and 14:* 2 mL solution to be taken orally once per day in the mornings	*Day 00 and 14:* 1 tablet to be taken orally once per day in the mornings
Arm 3 (BTZ_{250mg})	*Day 01-14:* 1 tablet to be taken orally once per day		*Day 00 and 14:* 1 tablet to be taken orally once per day	*Day 00 and 14:* 1/4 tablet to be taken orally once	*Day 00 and 14:* 2 tablets to be taken orally once	*Day 00 and 14:* 10 mL solution to be taken orally	*Day 00 and 14:* 2 mL solution to be taken orally once	*Day 00 and 14:* 1 tablet to be taken orally once per day

	in the mornings*		in the mornings	per day in the mornings	per day in the mornings	once per day in the mornings	per day in the mornings	in the mornings
Arm 5 (BTZ_{XXXmg})****	*Day 01-14:* Respective no. of tablets to be taken orally once or twice a day		*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Arm 6 (BTZ_{XXXmg})****	*Day 01-14:* Respective no. of tablets to be taken orally once or twice a day		*N/A*	*N/A*	*N/A*	*N/A*	*N/A*	*N/A*
Arm 4 (control)		*Day 01 - 14:* 3 – 5 tablets to be taken orally once per day in the mornings**						

** BTZ-043 dosage in Stage 2 has been determined by the TSC after review of the safety data from Stage 1*
*** daily doses to be given adapted to body weight to fasting patients, in accordance with South African Guidelines for treatment of TB (38-54 kg: 3 tablets; 55 - 70 kg: 4 tablets; > 70 kg: 5 tablets). Weights are to be rounded off to the nearest integer.*
**** Patients will be randomized to receive either the probe drug cocktail or Dolutegravir at a ratio of 2:1, favouring the probe drug cocktail*
***** as part of the probe drug cocktail*
****** Rifampicin 150 mg, Isoniazid 75 mg, Pyrazinamide 400 mg, Ethambutol 275 mg per tablet*
******* BTZ-043 dosage and administration in Arm 5 and Arm 6 will be determined by the TSC after interim analysis of the data of the first patients in Stage 2*

In order to achieve the most accurate results, the study personnel must ensure that **al**l study drugs have been taken according to schedule and time.
In case a participant starts vomiting shortly (within 30 min) after study drug intake, the following procedures apply:

7.3 Procedures in case of vomiting post-dosing

1. Note of date and time of vomiting and calculation of minutes since study drug intake.
2. Inspection of vomit, especially for remainders of study drugs.
3. Decision on re-dosing of the participant after assessment by the PI:
   - Re-Dosing of study drug: only if **all** tablets are still fully intact and not disintegrated **and** calculated time between study drug administration and vomiting **does not exceed 20 minutes**, the participant shall be re-dosed with the number of tablets that were found in the vomit in a fully intact state (not disintegrated).

OR

- Continuation without re-dosing: if **any** of the above **does not** apply, the participant will **not** be re-dosed again at this time point. Instead the participant will continue with the study procedures and will be administered study drugs as per protocol again at the next time point as described in the SOE.

4. Documentation of the procedures, including date and time of all occurrences, a description of the vomit and tablets, and decision taken in source data.
5. Documentation of the incident as an AE in the (e)CRF.
6. Information of the sponsor by Note-to-file accordingly within 48 hours of the incident.

7.4 Procedures to Assign Patients to Treatment Groups

After signing the informed consent form (ICF), patients receive a unique patient identification (ID) number at screening. This number consists of an allocated site number followed by a consecutive subject number. Each new patient is given the lowest available number from the consecutive numbers allocated to a study site. Once a number was assigned to a certain patient, this number may not be reused.

Allocation of patients will be carried out in two stages:

1st stage:

Patients will be allocated sequentially to 8 experimental cohorts, starting with cohort 1. For each cohort 3 patients will be enrolled to receive the investigational drug BTZ-043 in a pre-defined dose for 14 days according to the Schedule of Events. After safety data is available from at least 7 days of treatment, the TSC, composed of the national principal investigator (PI), the trial statistician and the sponsor representative will review safety data including clinical, lab and ECG. On this basis it will then be decided on dose escalation before starting the next cohort, as shown in Figure 3.

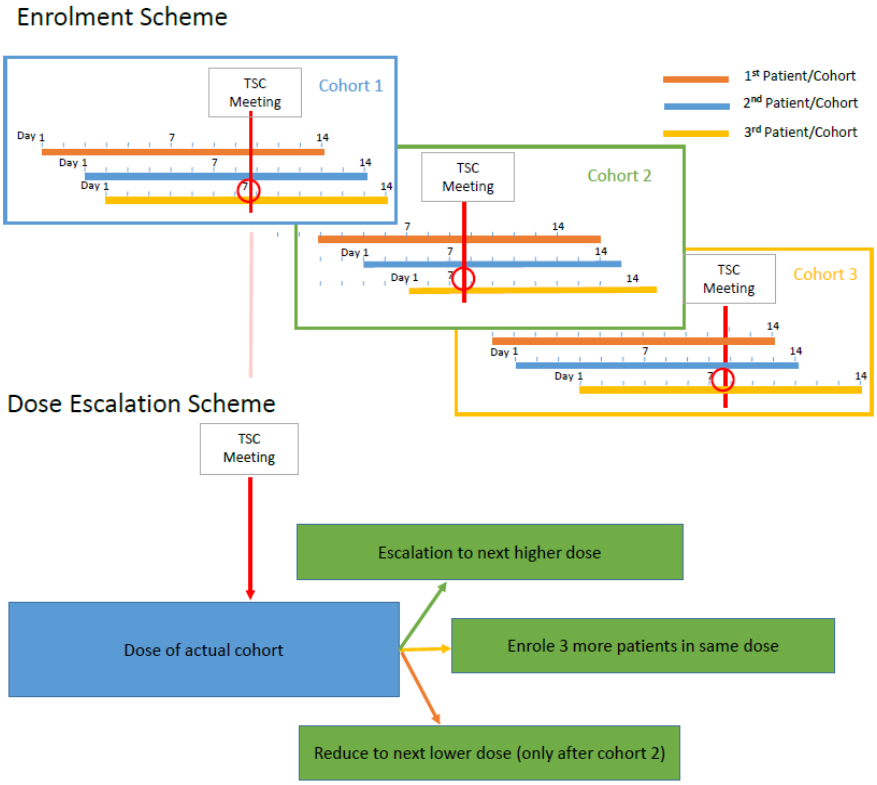
Stopping rules will be applied accordingly.

Dose escalation steps:

- Cohort 1: patients to receive 250 mg BTZ-043
- Cohort 2: patients to receive 500 mg BTZ-043
- Cohort 3: patients to receive 750 mg BTZ-043
- Cohort 4: patients to receive 1000 mg BTZ-043
- Cohort 5: patients to receive 1250 mg BTZ-043
- Cohort 6: patients to receive 1500 mg BTZ-043
- Cohort 7: patients to receive 1750 mg BTZ-043

– Cohort 8: patients to receive 2000 mg BTZ-043

Figure 3. Participant Enrolment and Dose Escalation in Stage 1



An interim PK-/PD-analyses will be performed at the end of the 1st stage. The TSC will review the safety data as well as the results of the interim analysis and decide on three different doses to be used in the 2nd stage of the trial.

2nd stage:

After completion of the 1st stage, when the highest possible dose of the investigational drug, that has proven to be safe during the 1st stage, is identified, the remaining patients will be recruited and randomised prospectively to one of four treatment arms at a ratio of 3:3:3:2 favouring the experimental treatment.
These patients will be prospectively randomised to receive 1000mg, 500mg or 250mg of BTZ-043, or to control medication.
If the TSC supports the decision for 2 additional arms of BTZ-043, these arm 5 and 6 patients will be recruited through random allocation after arm 1-4 are fully enrolled.
Only in patients receiving BTZ-043, blood samples will be collected for the pharmacokinetic characterisation of BTZ-043 and its main metabolites as well as for the determination of a potential food effect (stage 1) and alterations in the probe drug metabolism (stage 2).

7.5 Blinding and Unblinding Procedures during the Study

This study will be conducted with patients and physicians being aware of treatment allocation, since patients in the 1st stage will all receive the investigational drug BTZ-043 and since patients receiving Rifafour e-275® in the control arm will produce discoloured urine as a side-effect of the RIFs.
The personnel assessing patients' outcomes, like the microbiology and safety laboratory staff, will remain blinded to treatment assignment throughout the whole study. Every effort will be made to maintain this blinding.
Therefore, no procedures for unblinding patients nor investigators are necessary. The pk-laboratory will not be kept blinded.

7.6 Study Drug Packaging, Labelling, Distribution and Storage

A Study Drug Management Plan will describe all aspects of drug management in this study, including details on packaging, labelling, distribution, drug-dispensing, drug accountability and other drug-related procedures. A team of pharmacists, including a pharmacist at each study site, will be responsible for study drug management.
The Sponsor will supply sufficient quantities of the study drugs to allow completion of this study, including spare drugs.
The overall intent of the labelling of the study drugs is to ensure the protection of the trial participants, to ensure traceability and identification of the drugs and trial at all times, to facilitate the proper use of the drugs, and to comply with national and international regulations on investigational drugs. The study drugs will be labelled for the study according to The Rules Governing Medicinal Products in the European Union, Annex 13 of GMP, and to national labelling requirements of the study sites.
All study drugs must be kept in secure cabinets or rooms with access restricted to designated study personnel. Medication will be stored at appropriate conditions at designated temperatures, protected from light and moisture. A temperature monitoring system will be in place to monitor appropriate storage conditions and record possible deviations. Alternative storage facilities are in place, in case of major failures or deviations from these conditions.
The storage, handling and dispensing of study drugs for individual patients will be performed and recorded as described in the Drug Management Plan. Dispensing at each site will be supervised by a pharmacist. Dispensing will only be performed by licensed and trained study personnel.

The IMP will be manufactured by Gen-Plus GmbH & Co. KG and will be provided in High-Density Polyethylen (HDPE) bottles. Each bottle will contain 60 tablets á 250 mg BTZ-043.

The control medication in stage 2 and the probe drug cocktail medication are licensed in South Africa and will be purchased locally.

Tolbutamide is not approved in South Africa, but several formulations of tolbutamide are approved in Europe. Approved tolbutamide will be imported into South Africa for this study.

7.7 Measurement of Patient Compliance

All study drugs will be administered by the investigator or designated study personnel. Intake will be observed by study staff during the study visits in the mornings. Hands and mouth control will be performed after each study drug administration. Furthermore, treatment adherence will be assessed by pill counting at every visit. Patient compliance will be documented in the source documents and in the eCRF.

7.8 Study Drug Accountability

The study pharmacists will be responsible for maintaining accurate records of receipt and destruction of all study drugs as well as of all medication dispensed to and used by each patient in the "Study Drug Inventory Log". The records should reflect the overall quantity of study drugs at site. Furthermore, the pharmacist will maintain individual records of study drug dispensing and return for each patient (Study Drug Dispensing and Accountability Forms).
At the completion of the study, all unused BTZ-043 will be returned to the sponsor or a CRO designated by the sponsor or is destroyed, once drug accountability is complete and checked by the monitor.
All other unused study drugs may be used by the sites in routine patient care, if the brand of the drug is approved by host country's regulatory authority and after approval of the sponsor. If this is not the case, the same provisions for return and destruction as described for BTZ-043 will take place.

7.9 Retention of Testing Drug Samples

Sufficient quantities of each study drug will be kept by the sponsor to reconfirm specifications should the need arise. These samples should be retained until the analysis of trial data is complete or as required by applicable regulations, whichever is longer. After this period, retention samples will be destroyed following national regulations.

7.10 Post-study access to treatment

After participants have completed 14 days of study treatment, they will be referred to continue standard of care TB-treatment for 6 months at a government health facility. It is advised that participants complete a full six-month course of first line treatment, according to South African National TB Guidelines. This is to be laid down in a site-specific procedure following local guidance.

7.11 Concomitant and Prohibited Medication

Significant concomitant use of one or more of agents of the following classes will be evaluated by the sponsor medical expert and may lead to exclusion of the patient from treatment. Excluded patients will be taken off-IMP and their participation in the study may be stopped. Their experimental treatment may be stopped, and they may be continued on standard TB treatment according to national guidelines.
An overview of drugs allowed as concomitant medication and prohibited medication can be found in the following description:

7.11.1. Prohibited medication: anti-tuberculosis agents

Use of drugs with an action on MTB complex, **in addition** to study treatment, is prohibited while participants are receiving study treatment in both stages and all arms, intervention and control arm. This includes, but is not limited to amikacin and other aminoglycosides, cycloserine, EMB, ethionamide, prothionamide, linezolid, INH, LZD, para-aminosalicylic acid, RIF, rifabutin, rifapentine pyrazinamide, streptomycin, kanamycin, thioacetazone, capreomycin, fluoroquinolones, thioamides.

7.11.2. Prohibited medication: QT-prolonging medication

Concurrent treatment with QTc-prolonging agents (other than the study drugs) is prohibited for participants in all treatment arms in this study until visit 16 at day 14, as this could influence the safety assessments of novel treatment combinations and put participants at risk. QTc-prolonging agents include but are not limited to amiodarone, bepridil chloroquine, chlorpromazine, cisapride, clarithromycin, disopyramide dofetilide, domperidone, droperidol, erythromycin, halofantrine, haloperidol, ibutilide, levomethadyl, lumefantrine, mefloquine, mesoridazine, methadone, pentamidine, pimozide, procainamide, quinidine, quinine, sotalol, sparfloxacin, terfenadine, thioridazine, voriconazole during study participation.
Significant concomitant use of one or more of these agents will be evaluated by the sponsor medical expert and may lead to exclusion of the patient from treatment. Excluded patients will be taken off-IMP and will be follow-up according to protocol.

7.11.3. Prohibited medication: CYP450 inhibitors/inducers

The potential of BTZ-043 to influence concomitant medications by inhibiting metabolizing enzymes is likely low based on in-vitro studies, but cannot be effectively ruled out at this point. Enzyme induction and inhibition potential will be assessed in this study. Further, BTZ-043 is metabolized by liver microsomes and could therefore be influenced by drugs that affect the liver microsomal enzyme system.
A change in activity of these hepatic enzymes can change the drug concentrations in blood and tissue and thereby influence safety and efficacy readouts. All drugs that would lead to a

substantial change in activity of these enzymes are prohibited; and participants may not be included into the study if receiving such drugs at screening, within 2 weeks prior to the first dose of study treatment or if it is likely that these drugs will be needed during study treatment. Patients who are enrolled and on study drugs, and a need arises to treat with any of those drugs during the treatment phase of the trial need to be discussed with the sponsor medical expert. Patients requiring treatment with any drug(s) or substance(s) known to be strong inhibitors or inducers of cytochrome P450 enzymes are prohibited in the study, this includes grapefruit containing foods/beverages and St. John's Wort.
A list for these is provided under https://drug-interactions.medicine.iu.edu/Main-Table.aspx, "inhibitors" and "inducers".

7.11.4. Prohibited medication: antacids/antipeptic drugs

In preclinical studies, famotidine, when given before the administration of BTZ-043, reduced bioavailability of BTZ-043 substantially.
Therefore, all drugs that increase gastric pH-levels, like antacids, H2 antagonists (e.g. ranitidine, famotidine) and proton pump inhibitors (e.g. omeprazole, pantoprazole, lansoprazole) are prohibited in participants, from at least two days before planned start of dosing.

7.11.5. Prohibited foods/beverages

During Hospitalization, patients must abstain from food and drinks, which may interact with circulatory, gastrointestinal, hepatic or renal function (e.g. alcoholic or methylxanthine*-containing beverages or grapefruit juice)

*namely 1,3,7-trimethylxanthine (caffeine: coffee, tea, cola, energy drinks), 3,7-dimethylxanthine (the obromine: cocoa, chocolate), and 1,3-dimethylxanthine (theophylline: traces in tea).
Decaffeinated beverages contain residual caffeine and must also be avoided.

These substances may interfere with measurements of the probe drug cocktail, or may interfere with metabolism of the IMP.

8. Participant Enrolment

Patients will be invited to be screened for inclusion in the trial if they are suspected to have pulmonary TB or have an established diagnosis by smear microscopy, GeneXpert or chest X-ray, done within the government or private health sector.
A total of up to 105 patients will be enrolled at 2 sites in Cape Town / South Africa. Patients will be assigned to study treatment only if they meet all of the inclusion criteria and none of the exclusion criteria.

8.1 Recruitment Procedures

Recruitment might be enhanced by individual and community awareness of the study and/or TB in general through the following materials, including:

- Public announcements through advertisements, posters and radio announcements
- Information leaflets distributed to healthcare providers, to be handed to newly diagnosed TB patients

All materials will be used only upon approval of the ethics committees and/or regulatory authorities relevant for this trial.

8.2 Patient Informed Consent

Patients with a suspicion of pulmonary TB, either by clinical findings or diagnostic statement/lab results, will be invited to be screened for inclusion in the study. They will be given an ICF of the study and the PI or a designated person will fully inform the patient about the anticipated benefits and the potential risks associated with the protocol procedures. The language used will be as non-technical as possible and the patient will not unduly be influenced to participate in the study.
Patients will be informed that screening includes collecting sputum samples, blood and urine samples, a chest X-ray, ECG registration and pregnancy testing, if applicable. Blood analysis will include testing for HIV. The patient will be encouraged to receive their HIV result, but may chose not to be informed of the result. HIV seropositive individuals, who wish it, will be referred to the local HIV services. Patients will be told that agreeing to be screened does not mean that they have to join the study, and that participation in the study will require at least 15 days of hospitalization and good adherence during the whole study period. Patients will be informed that they will be free to withdraw from the study at any time, and a withdrawal will have no negative effects on them receiving standard care afterwards.
Written informed consent must be obtained from every patient prior to any procedures being done specifically for the study. For illiterate patients, study information is given in the presence of an impartial, literate witness, who will read the information sheet to the patient

or will witness the complete reading of the information sheet to the patient. The patient will give consent by thumb printing the ICF (or signing in case of some literacy) and the witness states that free, informed consent has been given by his/her signature on the ICF.
The signed original ICF will be kept with the patient's medical records at the site. A second original or a photocopy of the signed ICF will be given to the patient or to the patient's legally acceptable representative.
The ICF will be provided to the investigator by the sponsor. If any modifications to the form are proposed by the site, the consent form must be submitted to the sponsor for approval prior to submission to the ethics committee. The ICF will be revised whenever new important information becomes available and will undergo ethics committee review. The ICF can only be used after approval of the ethics committee. All active patients must then sign additionally the revised form, after ethics approval was received.

8.3 Exclusion of particular groups

Minors below 18 years are excluded from the study. TB in children is different in diagnosis and disease course from adult disease. Therefore, this age group will not participate in this trial. For the investigational drug, no data regarding safety in juvenile animals or in children is available so far.
Patients infected with HIV are excluded from the trial, since this is an early stage study and safety signals originating from a concomitant disease have the potential to confound decisions on drug development. Further, anti-HIV treatment could potentially interact with the PK of BTZ-043. This study aims at characterising such interactions by using the probe drug cocktail and dolutegravir, so that HIV co-infected patients on ART can safely be included into future trials with BTZ-043, in line with PanACEA commitment to make new TB treatments available to people living with HIV.

8.4 Vulnerable patients

Patients who are unable to give free, informed consent (e.g. mentally impaired persons, prisoners) will be excluded from the trial, as their unconstrained agreement to trial participation and procedures cannot be ascertained, and compliance may be suboptimal.

8.5 Patient Withdrawal

A patient may decide to withdraw consent and therefore to resign from the trial at any time and for any reason. The investigator may also withdraw a patient from the experimental treatment or from the entire trial for any of the following reasons:

- Major protocol deviation
- If, for safety reason, the investigator concludes that continued participation in the study would not be in the participant's best interest

- Participant requires a medication that is prohibited by the protocol

The investigator will also withdraw a patient upon request of the sponsor or if the trial is terminated as a whole. If a serious adverse event (SAE) occurs, the PI will discuss it with the sponsor. A patient, who is discontinued due to an AE, will be followed up as described under the section "Adverse Events", Chapter 9, page 79.
When a patient withdraws from the study, the reason(s) for withdrawal shall be recorded by the investigator on the relevant page of the CRF.

On the date of withdrawal: If possible, participants should have all assessments scheduled for Day 14 (visit 16) and Day 15 (visit 17) completed on the day they leave the site. These should include vital signs, complete physical examination, 12-lead-ECG, concomitant medication, assessment of AEs and ophthalmological examination. If PK sampling is already ongoing that day, continuation of collection of PK-samples is appreciated to complete the 24-hour post dose sampling, if the participant is willing to do so. For withdrawals on other study days, no unscheduled PK sampling is requested.
Recent safety laboratory results from the day of leaving the site or the day before should be available to make sure, that no adverse findings are missed that could put the participant at risk. Unscheduled sampling is advised. In female participants of childbearing potential, a serum pregnancy test should be requested, if possible.
Follow-up visit: If possible, a follow-up visit should be scheduled 7 days (+/- 3 days) after discharge/withdrawal. During this visit all procedures as described in section 5.5.5 "Follow-up Period" should be carried out, i.e. vital signs, symptom related physical examination, follow-up of former AEs and assessments of new AEs, incl. blood tests to follow up on past abnormal results and new AEs, as per the investigators discretion.
Patients who withdraw from the study should undergo all end-of-study assessments. Patients who do not return for final assessments will be contacted by site personnel in an attempt to have them comply with the protocol.
The study site will undergo maximal efforts to contact and trace participants who are lost to follow-up.

8.6 Stopping Rules

The decision to halt the study will be made on cumulative information of adverse events by the sponsor. The sponsor will receive recommendation by the TSC.
If any of the below conditions are met, the sponsor in consultation with the PI, will suspend enrolment and perform a full safety review. For this, the sponsor may consult external experts. Enrolment would only resume after review by the TSC and a decision resulting in a recommendation to the sponsor to permit further trial inclusion.

Cohort stopping rule during the 1st stage:

If ≥ 1 participants experience an SAE (not including prolongation of hospitalisation) at least possibly related to BTZ-043, all patients receiving this or higher doses of IMP will stop treatment. No dose escalation will be performed.

Stopping rules during the 2nd stage:

If ≥ 1 participant meets individual patient stopping criteria for discontinuation of IMP, an ad hoc meeting of the TSC will be installed to evaluate patients' safety and decide on further dosing or stopping of patients.

8.7 Additional Individual Patient Stopping Criteria

Blood pressure Stopping Criteria:

- A mean systolic blood pressure >180 mm Hg or <80 mm Hg, and/or a mean diastolic blood pressure >110 mm Hg as measured by triplicate measurements
  - ➢ Patients will stop study treatments immediately and receive antihypertensive treatment. During follow-up, investigators should attempt to determine whether the condition normalizes after discontinuation of study treatment in order to better judge relatedness to IMP.
- A mean systolic blood pressure >160 mm Hg or <85 mm Hg for more than 12 hours, and/or a mean diastolic blood pressure >100 mm Hg for more than 12 hours as measured by triplicate measurements per time point, with control measurements after 4, 8 and 12 hours
  - ➢ in this case, study drug will be discontinued for 24 hours and the patient will be re-assessed before the next dosing.
- Continued hypertension after re-assessment: participants who develop persistent hypertension ≥ 160/100 mmHg after evaluation and adequate antihypertensive treatment, including those, who have undergone a re-challenge with study drugs, will discontinue all study treatment and complete TB treatment according to national TB program guidelines. These participants will receive follow-up to determine whether the condition normalizes after discontinuation of study treatment.

ECG Stopping Criteria:

A patient that meets **either** bulleted criterion below will be withdrawn from dosing (withdrawal of patients is to be based on an average QTcF value of triplicate ECGs):

- QTcF >500 msec,
- Change from baseline: increase in QTcF >60 msec

➢ In this case, the patient will be monitored closely with at least daily ECGs until the abnormality abates. Study drugs and other potentially offending drugs will be withheld. Blood electrolytes (mainly Mg+, Ca++, K+) will be measured and abnormalities corrected, after discussion with the sponsor medical expert.

As soon as normal values are restored, study drugs might be restarted in close discussion with the sponsor medical expert and after approval of the sponsor or the sponsor delegated person. The first drug to be started shall be BTZ-043, since this has no signal of QT prolongation to date.

Hepatotoxicity stopping criteria: these follow the FDA guidance on evaluation of drug-induced liver injury [19]. A patient should discontinue study drug if:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× ULN and/or alkaline phosphatase (ALP) >5×ULN for >7 days.
- ALT or AST) >8× ULN and/or alkaline phosphatase (ALP) >8× ULN
- ALT or AST >3xULN and (total bilirubin (TBL) >2xULN or INR >1.5
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

Other:
Severe signs or symptoms, or significant changes in any of the safety assessments that put the safety of the individual at risk (e.g. ECG, vital signs, laboratory tests etc.), in consultation with the sponsor medical expert.

9. Adverse Events

9.1 Definitions

For safety monitoring and reporting purposes, a drug related AE is defined as an adverse event that is judged to be definitely, probably or possibly related to (one of) the study drug(s). Adverse events will be graded for severity according to the CTCAE 5.0 grading system [20].
The following will be analysed:

- Proportion of adverse events of Grade 3 or Grade 4 severity.
- Proportion of adverse events possibly, probably or definitely related to study drugs.
- Proportion of treatment discontinuations or interruptions related to adverse events
- Specific ECG endpoints:
  - Frequency, severity and type of ECG alterations
  - Changes to PR, RR, QRS, QT, Fridericia-corrected QT [QTcF]
  - Proportion of participants with QTcF > 500ms on treatment
  - Proportion of participants, who experience a prolongation of QTcF > 60ms relative to baseline measurement
- Specific blood pressure endpoints:
  - Proportion of participants, who experience a medium systolic blood pressure >180 mm Hg or <80 mm Hg, and/or a medium diastolic blood pressure >110 mm Hg as measured by triplicate measurements

- Proportion of participants, who experience a medium systolic blood pressure >160 mm Hg or <85 mm Hg for more than 12 hours, and/or a medium diastolic blood pressure >100 mm Hg for more than 12 hours as measured by triplicate measurements with control measurements after 4, 8 and 12 hours

Definitions of dose limiting toxicity:

- For hepatotoxicity, ECG and blood pressure, dose limiting toxicities are defined as under individual patient stopping criteria
- For all other toxicities, the following applies:
  - moderate (grade 2) or higher grade toxicity (graded following Common Terminology Criteria for Adverse Events (CTCAE) V5.0), that is at least probably related to IMP
  - grade 3 or higher AEs that are at least possibly related to IMP

Term	**Definition**
Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered.
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the information about the medicinal product in question set out in the Investigator Brochure or Summary of Product Characteristics (SmPC) for that product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)	Respectively any adverse event, adverse reaction or unexpected adverse reaction that: • results in death • is life-threatening* • requires hospitalization or prolongation of existing hospitalization** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalization is defined as an inpatient overnight admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Hospitalizations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE.

9.2 Collection of Adverse Event Information

Adverse events will be collected by the investigator from the time a participant is enrolled in the trial and any study specific procedures were performed (further information in 9.3. Clarifications and Exceptions)Patients will be instructed during the informed consent counselling to report all AEs to the investigator, also between study visits and if not directly asked for. Patients will be asked to contact the investigator outside the schedule in case of a new complaint, or worsening of an existing complaint, if they feel that it is severe. At every study visit, patients will be asked to describe their complaints and report new occurrences. Physical examination findings, vital signs and laboratory information will be gathered as described in section 'Safety Assessments', page 58. Additional investigations will be ordered by the investigator, if they are in the subject`s best interest.

9.3 Clarifications and exceptions

Occurrences will be registered as AE from administration of the first dose of study drugs. All events that occur or are elicited before administering any study drugs, e.g. screening laboratory abnormalities qualifying as Adverse Events, will be recorded as medical history. If such events meet criteria for seriousness, they will nevertheless be reported as SAEs without impact on the continuation of the study.
Abnormalities which are not clinically significant as per the qualified judgement of the investigator do not constitute adverse events and are not recorded and reported as such. However, these abnormalities may be analysed and reported in the study report.

9.4 Assessment of Causality

The investigator will review each AE and assess its relationship to study treatment based on all available information at the time of the completion of the CRF.
Each sign or symptom reported will be graded on a 5-point causality scale (see below). Additionally, the date and time of onset, relationship to the study drugs, duration, action taken, and outcome (resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up)) of each event will be noted.

The following definitions for rating attribution/causality will be applied:

Relationship	Description	Event Type (if Serious)
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).	Unrelated SAE
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).	SAR
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	SAR
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

Factors to be considered in judging relatedness include:

- temporal sequence from drug administration
- recovery on discontinuation (de-challenge), recurrence on re-administration (re-challenge)
- underlying, concomitant, intercurrent disease
- concomitant medication or treatment
- known response pattern for the drug class the participant is receiving
- exposure to physical and/or mental stresses
- pharmacology and PK of the medication used

9.5 Assessment of Severity

Severity of AEs will be classified following the U.S. National Institutes of Health Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, available online at http://evs.nci.nih.gov/ftp1/CTCAE, [20]. If a specific event is not contained in this compendium, the following generic definition, which is also provided by the CTCAE system, shall be applied for such events:

- Grade 1 = Mild: i.e. asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2 = Moderate: i.e. minimal, local or non-invasive intervention indicated; limiting age appropriate instrumental activities of daily life (ADL)*

- Grade 3 = Severe: i.e. significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
- Grade 4 = Life-threatening: urgent intervention indicated
- Grade 5 = Death: related to AE

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, work or farming, managing money, etc.*
***Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden*

9.6 Adverse Event Recording

Any AE observed by the investigator or reported by the subject will be recorded in the source data and on the AE page in the eCRF. The investigator will review each AE and assess its relationship to the study treatment based on all available information at the time of the visit. The following information will be recorded:

- Diagnosis of the AE, if possible. In the case where an overall diagnosis cannot be made, each specific sign and/or symptom will be recorded as an individual AE (where possible CTCAE wording should be used)
- Date of onset, stop date and duration, if applicable
- Severity grade
- Seriousness
- Relationship to IMP/non-IMP study drugs
- Action taken with IMP/non-IMP study drugs
- Other action taken
- Outcome

9.7 Serious Adverse Event Reporting

Adverse events will be recorded by the investigator from the time a participant is enrolled in the trial.

Any AE which is serious, or which is potentially serious (if a decision cannot be taken due to a lack of information) must be reported by the investigator to the Sponsor within 24 hours of the site first being aware of the SAE, whether or not the event is deemed drug-related. Medical review will be done by the Sponsor Medical Expert.
Information about SAEs will be provided by the investigator in a detailed written and signed SAE form, including the investigator's judgment of the seriousness criteria and the relationship with the study drugs.

To update or add information to a reported SAE, the investigator will use a new SAE form, stating that this is a follow-up to a previously reported SAE and send it within 24 hours after receiving the new information to the same contact.
Medical review of the case will be done by the Sponsor Medical Expert together with the National PI, and the SAE will be evaluated for expectedness and relationship to the study drugs. If additional information is needed to complete the profile of the reported SAE, this will be requested from the Investigator.
For unexpected treatment-emergent SAEs (SUSARs) the sponsor/designee will complete a standardized form by the Council for International Organizations of Medical Sciences (CIOMS) and forward to investigators, ethics committees and regulatory authorities in accordance with local requirements and ICH guidelines.

9.8 Clinical Laboratory Adverse Events

It is the investigator's responsibility to review all lab results as they become available. This review must be documented by the Investigators' dated signature on the laboratory report.
For each abnormal result, the investigator needs to ascertain if this is a clinically significant change from baseline for that individual patient. This determination, however, does not necessarily need to be made the first time an abnormal value is observed. The investigator may repeat the test or request additional tests to verify the results.
All changes in lab results, which the investigator feels are clinically significant, will be reported as AEs.

9.9 Disease under Study

Symptoms of the disease under study, i.e. pulmonary TB, experienced by the subject during study participation will be assessed by the investigator. If the symptoms have worsened whilst the subject is on the study, and the investigator assesses it as clinically significant, it will be recorded as an adverse event. If there is no clinically significant change and the investigator assesses the symptoms as due to the subject's TB, it will not be recorded as an AE. If the Investigator is unsure as to whether the symptom is clinically significant or not, it is to be classified as significant and reported as an AE.

9.10 Follow-up of Adverse Events

9.10.1 General Follow-up of Adverse Events

During and following a patient's participation in a clinical trial, the investigator must ensure that adequate medical care is provided to the patient for all AEs, including significant abnormal laboratory values. The investigator should inform the patient to contact the site, when medical care is needed for any AE the patient becomes aware of.

All non-serious AEs classified as grade 3 or worse, or definitely/probably/possibly related to IMP must be followed until the AE has resolved, or until there is no further change likely to the participants' condition.
Cases of pre-existing chronic conditions or if the patient dies from another event can be closed with an outcome of "unchanged". In case a pre-existing conditions worsens during the treatment or follow-up period, this has to be recorded as an AE and followed-up accordingly.

All other non-serious AEs must be followed until the outcome of the event is "improved" (for chronic conditions), "resolved" or until the last study visit, and all queries on these AEs have been resolved. If the patient dies from another event, the case can be closed with an outcome of "unchanged".

All Serious AEs must be followed until the outcome of the event is deemed "resolved", "unchanged" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer or if the patient dies from another event can be closed with an outcome of "unchanged".

9.10.2 Follow-up of Post-Trial Adverse Events

Any new SAE reported by the patient to the investigator, determined by the Investigator to be causally or possibly related to the use of the IMP, that occurs until 30 days after the last scheduled visit or last intake of study drugs, whichever is the later, must be reported by the investigator to the Sponsor Medical Expert within 24 hours of learning of its occurrence. Any SAEs experienced after this 30 day period should be reported only, if the investigator suspects a causal relationship to the study drug.

10. Pregnancies as Adverse Events

10.1 Pregnancy Procedures

All women of childbearing potential will be instructed to contact the investigator immediately if they suspect they might be pregnant during the trial (for example, missed or late menses). If pregnancy is suspected while the patient is receiving experimental study treatment, this will be withheld immediately until pregnancy can be ruled out with certainty.
If pregnancy is confirmed, experimental treatment will be permanently discontinued in an appropriate manner. The patient should complete her TB treatment course following the host country's national guidelines.

10.2 Pregnancy Reporting

The investigator must immediately notify the sponsor of any pregnancy in a study subject. The pregnancy must be recorded on the pregnancy form and forwarded to the sponsor. Expedited reporting of pregnancy to regulatory authorities is necessary in case of a pregnancy complication fulfilling the criteria for Serious Adverse Events.
Protocol-required procedures for trial discontinuation must be performed unless contraindicated by the pregnancy (e.g. X-ray is contraindicated). Other appropriate pregnancy follow up procedures should be considered if indicated. In addition, the investigator must report to the sponsor for follow up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants must be followed for a minimum of 6 months. Congenital malformations are to be reported as Serious Adverse Events.

11.Statistical Considerations

11.1 Sample size determination

This is a Phase IIA trial to investigate the EBA and safety, tolerability and PK of one, or optionally, two daily doses of BTZ-043.
15 patients per treatment group is typical with other trials of this type and accounts for the possibility of up to 3 drop-outs per group, which based on previous studies of this type conducted at these sites, represents a conservative estimate of the expected drop-out rate.

With our study design, we would expect to have 24-33 patients **in the first stage** of the study leaving 44-53 in the second stage of the study, leading up to a total of 77. **In the second stage**, we would therefore expect 20 patients (up to 9 from stage 1 and at least 12 from stage 2) on the highest dose at the target toxicity level (TTL) and 15 patients each on two other dose levels selected in stage 1 plus 8-10 patients in the control arm.
If the TSC decides for additional dose groups of BTZ-043, the total number of enrolled patients in the study may be increased (see section 7.4).
Previous EBA studies indicate that the between patient standard deviation of logCFU can be approximately 0.2. Therefore, assuming similar variability in the new trial the expected standard errors of group mean EBA and corresponding width of 95% confidence intervals are in the Table below.

Table 4. Expected Standard Error of Group mean log CFU and confidence intervals

Group size	Standard error	Width of confidence interval
15	0.052	0.101
10	0.063	0.124

We therefore expect our total sample size of 77 to give around 20 patients on the target toxicity level (across both stages) which is adequate to describe EBA and safety in order to select dose(s) for subsequent clinical development of BTZ-043.

At the time of the protocol amendment (Version 4.0), the stage 1 has been completed, with a total of 24 patients enrolled. The resulting sample size for Arms 1-4 in stage 2 is 14 patients for each experimental arm, and 11 patients in the control arm, a total of 53, with a total initial sample size of 77 patients. For every additional arm we will enrol an additional 14 patients, potentially increasing the total sample size from 77 to up to 105 patients.

11.2 Populations to be analysed

Intent-to treat (ITT) population: The ITT population will consist of patients in the groups to which they were randomly assigned.

Safety Population: The safety population will be defined as all patients who received any study drug

The Statistical Analysis Plan (SAP) will define the criteria for the exclusion of patients from any of the above mentioned analysis populations and will be finalized prior to database lock.

11.3 Statistical methodology

Baseline characteristics, such as demographic and analytical data will be summarized using descriptive statistical methods. Continuous data will be summarized using the mean, the median, standard deviation, the range (minimum and maximum value). Categorical values will be summarized using frequency counts and percentages.

11.4 Efficacy Analysis

The bactericidal activity of the IMP against MTB will be determined as the change in logCFU (solid media), or the change in days to positivity on MGIT over time (liquid media).

This is a descriptive study with no inferential statistics or hypothesis testing. There will therefore be no p-values presented, except in model building for comparing the fit of statistical models. Point estimates with standard errors or confidence intervals (as appropriate) will be presented. Data from patients on the control group will be included in the analysis and reported to confirm acceptable methodology and conditions for susceptibility testing. Results from the experimental groups will not be compared to that of the control group in the primary analysis, other than descriptively.
Secondary analyses will present estimates of differences from the control with confidence intervals as appropriate.

The standard EBA is the rate of change over the first two days, but it has been demonstrated for many TB drugs that the rate of change in bacterial load varies over time, and bactericidal activity may become evident only some days into the trial depending on the drug's pharmacokinetic properties. The decline in logCFU may therefore be linear, piece-wise linear (sometimes described as 'bilinear') or non-linear over each of the three time periods.

Various methods will be used to explore different shapes of the decline in logCFU. These include linear and restricted cubic splines in mixed effects models to explore non-linearity, linear mixed effects models for linear models and non-linear mixed effects parametric models (such as the biexponential model) as appropriate. Due to the small number of patients, it may not be possible to fit non-linear mixed effects models to the data. The estimated slope or slopes from the selected model will be summarized for each dose group.

11.5 Safety Analysis

11.5.1 Bayesian Prior for Dose-Toxicity Model

The CRM algorithm requires that a Bayesian prior for the dose-toxicity model be pre-specified. The prior for this study was determined from pre-clinical studies of BTZ-043 and in discussion with clinicians and statisticians. A weak prior was selected as limited information on the dose-toxicity relationship was available prior to study start and it was therefore desirable that the data collected took considerably greater precedence than prior opinion.

The Bayesian prior used for this design was based on the two-parameter logistic model assuming a linear slope with toxicity rate of 1% at the lowest dose (3 pseudo-observations) to 20% at the highest dose (3 pseudo-observations). The 95% pointwise confidence band (normal approximation) at the highest dose for this prior is very wide at (1%, 81%) reflecting the weak prior information that has limited impact on the dose-toxicity relationship once more than one cohort has been enrolled.

11.5.2 Safety Variables

ECG analysis

QT and QTc data will be analysed categorically based on the number and percentage of patients classified in each category by treatment group. QTc data will be presented for Friderica's corrections (QTcF).

Post-baseline QT and QTc intervals will be classified into the following categories:

- QT/QTcF < 450 ms
- 450 ms <QT/QTcF <480 ms

- 480 ms < QT/QTcF < 500 ms
- QT/QTcF > 500 ms

QTc changes from baseline will be classified into the following categories:

- decrease (an increase < 0 ms)
- increase < 30 ms
- >30 ms and < 60 ms
- increase >60 ms

Adverse Events

The incidence of adverse events and their relatedness to experimental treatment will be summarised by treatment group.

11.5.3 Methods for Safety Analysis

Binary and categorical variables will be tabulated by treatment arm. Continuous variables will be summarised with location (such as mean or median) and precision (such as standard error or inter-quartile range) summary estimates.

Patients with worsening condition from baseline on any variable will be described and tabulated. The following variables will be analysed:

- Laboratory Parameters: a list of safety laboratory parameters collected in the trial is described under “Safety Laboratory”, page 59.
- Physical Examination incl. neurological examination
- Vital signs

11.6 Pharmacokinetic Analysis

The PK of BTZ-043 and its two major metabolites BTZ-045S and M2, and other metabolites of interest, after a single dose and split-dose and at steady state will be evaluated by measuring the following parameters:

- area under the plasma concentration curve from dosing to the end of the dosing interval (AUC0-24) and to infinite (AUC0-inf)
- observed maximum concentration (C_{max})
- time to reach C_{max} (T_{max})
- minimum observed plasma concentration 24 hours following the last dose (C_{min})
- Clearance (Cl)
- Volume of distribution (Vd)
- Elimination half-life ($T_{1/2}$)

- Relation of efficacy measurements (pharmacodynamics) to pharmacokinetic indices of BTZ-043 and its metabolites (AUC, C_{max})

Furthermore, a population PK-analysis of BTZ-043 and its metabolites will be carried out to quantify inter-individual variability, suitable for evaluation of alternative dosing regimens.

The effect of food on the exposure of the BTZ-043 and its metabolites will be determined by evaluating the change in PK after a high-fat, high-calorie meal in comparison to the PK under fasting conditions during the 1st stage.

The effect on BTZ-043 at steady state on hepatic and P-gp enzyme activity (induction vs. inhibition) will be evaluated by measuring changes in PK of the probe drugs administered on day 0, and day 14 during the 2nd stage.

The effect of BTZ-043 on the exposure to a single dose of dolutegravir will be evaluated by measuring changes in exposure to dolutegravir (AUC up to 24h and until infinity), administered on day 0 and day 14.

11.7 Analysis of experimental efficacy endpoints

The molecular bacterial load assay (MBLA) and the sputum Lipoarabinomannan (LAM) assay will be evaluated against the conventional drug development endpoints, bacterial load measured in the BD MGIT™ liquid media culture system, and by solid media CFUs. Comparisons between methods will be performed on a per-sample, per-patient, and per-treatment arm basis.

11.8 Early Termination of the Study

If any the conditions specified under '8.6 Stopping Rules' are met, the sponsor, in consultation with the TSC, will perform a full safety review. For this, the sponsor may consult external experts. Enrolment would resume only after review of the adverse events by the TSC and a decision resulting in a recommendation to the sponsor to permit further study inclusion.
Should the TSC (if applicable) agree to early study termination, the patients should be seen as soon as possible and treated as described for prematurely withdrawn patients. The investigator will be responsible for informing IECs/IRBs and regulatory authorities of the early termination of the study.

11.9 Procedure for Accounting for Missing, Unused and Spurious data

Study data will, after being entered, be checked for consistency and completeness through programmed checks by the database, which will raise automatic queries. Further completeness and consistency checks will be performed by data management and any resulting queries will be sent through the database query system so as to leave an audit trail.

11.10 Procedures for Reporting Deviation(s) from the Statistical Analysis Plan

Any deviation from the Statistical Analysis Plan will be reported and explained in the study report.

11.11 Interim analysis

After the end of the 1st stage, an interim analysis of the safety data will be carried out, and upon this information the TSC will decide on the dosages of BTZ-043 for the 3 experimental intervention arms in the 2nd stage. Details of interim analyses for dose escalation and transition from stage 1 to stage 2 are described above.

After 5 patients per BTZ-043 receiving arm 1-3 complete treatment in Stage 2, an interim analysis will evaluate the bactericidal activity and PK data of the different doses of BTZ-043, given daily over 14 days. Upon this information, the TSC will decide on the implementation of up to two additional arms

12. Data Management

12.1 Data Collection

The investigator agrees to maintain accurate source data and Case Report Forms (CRFs). For each patient screened, an electronic CRF (eCRF) will be completed, even if the patient drops out at any time point during the study. All information from a performed visit must be entered in the eCRF.
All applicable eCRF pages must be completed for each participant, who has received any dose of study drug and has completed the study.
For participants who are prematurely withdrawn, the visits up to withdrawal plus the withdrawal visit need to be completed.
In the case of necessary corrections, all changes will be effectuated such that the first version is still legible, and the change is initialled and dated by the correcting person. Each completed eCRF must be reviewed, electronically signed and dated by the responsible PI or the sub-investigator in a timely manner.

12.2 Source Documents

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source documents will include, but are not limited to, progress notes, electronic data, screening logs and recorded data from automated instruments.

Study data will be collected and entered into the eCRF. Some data may still be captured entirely or partially on paper source documents and will manually be entered into an eCRF, including but not limited to:

- Informed Consents
- Chest X-ray images and reviews
- Sample collection data (will be on Lab Forms except for HIV and malaria test results)
- Safety and microbiology laboratory results and their review by the investigator.

All paper source documents and the electronic source documents pertaining to this trial will be maintained by the investigators. The investigator will be obliged to permit trial related monitoring, audits, Independent Ethics Committee/Institutional Review Board (IEC/IRB) review and regulatory inspections, providing authorized persons direct access to source data/documents.

13. Monitoring and Quality Assurance

13.1 Study Monitoring

One or more monitors will be assigned to the study. The monitor, as a representative of the sponsor, has the obligation to follow the study closely. The monitor will visit the site at regular intervals and will be in contact by phone and written communication, as required. Remote data review will be conducted during the COVID-19 pandemic, if on-site monitoring visits will be difficult.

Site investigators and designated study personnel will allow the monitors to inspect study documents, pertinent hospital or clinic records as well as site facilities, as required. All aspects of the study will be carefully monitored in order to ensure compliance with Good Clinical Practice and all applicable regulatory guidelines. The monitor will be responsible for verification of:

- adequacy of study personnel's qualifications as well as facilities
- the accuracy and completeness of the CRF entries, source documents and other study-related records
- appropriate study drug storage, usage and accountability
- informed consent procedures and patient eligibility
- appropriate adverse event reporting
- maintenance of the essential documents
- all other aspects of the study relating to protection of the rights and well-being of patients, accuracy of study data and adherence to the protocol

Source data verification will be carried out according to the monitoring plan.

The sponsor will provide a framework for maintenance of quality in performance and reporting of laboratory procedures through the laboratory monitoring plan.
The study database will only be closed after data has been verified by the sponsor, and all queries issued through data cleaning activities have been completed and resolutions documented.

13.2 Inspection of Records

The investigator will allow the sponsor, the sponsor's representatives, regulatory agencies and ethics committees access to all study records, if requested. The investigator will promptly notify the sponsor of any inspections scheduled by regulatory authorities or ethics committees and promptly forward copies of any inspection reports received to the sponsor.

13.3 Records Retention

The sponsor will keep essential study documents (including CRFs) other than subject's medical files until at least two years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP or for not less than 10 years after trial completion, whichever is longer.
Subject's medical files should be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.
These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

13.4 Confidentiality of Personal Data

All patient records, lab specimen etc. will be identified in a manner to maintain patient confidentiality and will be kept in a secure storage area with limited access. Each participant will be assigned a pseudonymous identification number. No data that could identify the patient other than this identification number (and the sex and date of birth) will appear on the eCRFs.
Data of study patients will only be used as defined in the ICF and in line with applicable data privacy regulations. Accordingly patient records may be reviewed by inspectors of regulatory authorities or ethics committees, study monitors and auditors, who ensure the quality of the study.
An individual's study data will not be released without the written agreement of the patient (or their legal guardian), except as necessary for monitoring and auditing by the sponsor or its representative, regulatory authorities or ethics committees, or in case of medical emergencies

when written consent cannot be obtained, as deemed in the participant' s best interest by the investigator.
This confidentiality will be in accordance to the recently instated EU Data protection Law (Regulation (EU) 2016/679) [21].

14. Ethical Considerations

14.1 Basic Principles

This study will be performed in accordance with the study protocol, the ICH-Harmonised Tripartite Guideline for GCP E6 (R1) (Consolidated Guideline E6, July 2002) and the Declaration of Helsinki (7th Revision, October 2013) as well as any other applicable national and other regulatory guidelines [22, 23].

14.2 Involvement of Ethics Committees and Regulatory Authorities

The protocol and the informed consent document to be used in this study must be submitted to the responsible investigator's ethics committee and regulatory authority, and also to the sponsor's local EC for approval. Written documentation of approval of both the protocol and the informed consent must be provided to the sponsor before starting the study.
The Investigator will ensure that the purpose of the study is explained to the patient and that written consent is obtained prior to participation in the study. The patient and the Investigator or his/her delegate will sign the consent prior to entry into the study.
The investigator will promptly report to the EC any changes in the research activity, deviations from the protocol and all unanticipated problems involving risks to human subjects or others, and will not make changes in the research without EC approval, except where necessary to eliminate apparent immediate hazards to human subjects.

14.3 Protocol Amendment Policy

Any change to the protocol will be effected by means of a protocol amendment. Any changes which affect participant safety or welfare will be submitted to the independent ethics committee/institutional review board (IEC/IRB) and regulatory authorities prior to implementation. The Investigator, IEC/IRB, and sponsor must agree on all amendments. No amendment will be implemented until approved by the relevant authorities and signed by all required parties. Exceptions to this are when the Investigator considers that the participant's safety is compromised.
Protocol amendments detailing minor administrative changes should be submitted by the Investigator to the IEC/IRB for notification purposes as appropriate.

14.4 Investigators' View of the Ethical Issues and Considerations

The investigator(s) participating in this study, as listed above, have had the opportunity to review the protocol outline.
The concerns and suggestions have been included into the final protocol.

14.5 Falsification of data

Any proven evidence of falsification of data will be dealt with in accordance with the policy of the sponsor and appropriate action will be taken.

15.Administrative Considerations

15.1 Trial Steering Committee

The role of the TSC is to provide overall supervision of the trial, final decisions on dose escalation during stage 1, oversight of safety of participants as needed. The TSC will formally report to the Sponsor. TSC specifics will be detailed and justified in a TSC charter. The TSC will at least consist of the national principal investigator (PI), the trial statistician and the sponsor representative.

15.2 Financing

The study sponsor is 'Klinikum der Universitaet Muenchen' (University Hospital, LMU Munich). The trial is conducted under the umbrella of PanACEA, the Pan African Consortium for the Evaluation of anti-TB Antibiotics. PanACEA is a not-for-profit consortium with the goal of shortening the treatment regimen of drug-sensitive TB.
Under the umbrella of the PanACEA consortium the University Hospital, LMU Munich has received sufficient funding by the European and Developing Countries Clinical Trials Partnership (EDCTP) and the German Ministry for Education and Research (BMBF) to ensure the appropriate funding of this study.

15.3 Study Registration

Before study start, the trial will be registered in clinicaltrials.gov, a WHO recognized clinical trials registry.
In addition, the trial will be registered in the South African National Clinical Trials Registry.

15.4 Patient Insurance and Compensation

The sponsor certifies that it has obtained or will obtain clinical trial insurance in line with the requirements in each country prior to study start. The insurance does not relieve the investigators of the obligation to maintain their own liability insurance as required by applicable law. The sponsor does not assume any obligation for the medical treatment of other injuries and illnesses.

15.5 Patient compensation for trial-related expenditures

Trial participants will receive a flat sum per trial visit (and per day spent in hospital) for out of pocket expenses, which covers loss of salary, travel to/from site and other miscellaneous cost, depending on the vote of the trial site's ethics committee. This sum will be laid down in the sites' informed consent documents to follow local practice and be approved by sites' ethics committees.

Should a trial participant have higher travelling expenses, these can be reimbursed at the discretion of the investigator. In such cases, receipts and considerations should be documented in the participant's records.
Since these payments are reimbursements of estimated cost, they do not constitute an undue incentive for trial participation.

15.6 Training for Staff Involved in the Study

During the initiation visit the monitor will ensure all involved site personnel is trained on all procedures relevant for their study responsibilities. Particular emphasis will be put on instructions for drug usage, administration, accountability and storage, lab procedures, data handling and safety procedures.

15.7 Publication Policy

After completion of the study, the data may be considered for presenting at a scientific conference or for publication in scientific journals. The sponsor will be responsible for these activities and will collaborate with the investigators to determine how the manuscript is written and edited, the number and order of authors, the journal to which it will be submitted and other related issues.
The results of the study will be published independent of the outcome – positive or negative - of the study.
Under certain circumstances, i.e. when the publication of particular findings (of an epidemiological, sociological or genetics study) may present a risk to the interest of a community or population or a racially or ethnically defined group of people, it may be considered inappropriate to publish findings.

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19.Appendix

19.1 Appendix 1. Package Insert RIFAFOUR®e-275 TABLETS

South African Electronic Package Inserts

INDICATIONS CONTRA-INDICATIONS DOSAGE SIDE-EFFECTS PREGNANCY OVERDOSE IDENTIFICATION PATIENT INFORMATION

RIFAFOUR®e-275 TABLETS

SCHEDULING STATUS:
S4

PROPRIETARY NAME
(and dosage form):

RIFAFOUR®e-275 TABLETS

COMPOSITION:
Each tablet contains:
Rifampicin 150 mg
Isoniazid 75 mg
Pyrazinamide 400 mg
Ethambutol 275 mg
Contains sodium ascorbate as anti-oxidant.

PHARMACOLOGICAL CLASSIFICATION:
A 20.2.3 Tuberculostatic combinations

PHARMACOLOGICAL ACTION:
Rifafour e-275 tablets is a combination of four first line agents used in the treatment of tuberculosis. Rifampicin is a semi-synthetic, broad-spectrum bactericidal antibiotic. Isoniazid is a synthetic, antitubercular agent which is bacteriostatic against semi-dormant bacilli and bactericidal against actively dividing mycobacteria. Pyrazinamide may be bactericidal or bacteriostatic, depending on its concentration and the susceptibility of the organism. Ethambutol is a synthetic, bacteriostatic antitubercular agent. All agents are readily absorbed following oral administration, with wide distribution to most tissues and fluids including cerebrospinal fluid.

INDICATIONS:
Initial phase treatment of pulmonary and extrapulmonary tuberculosis in new adult patients and re-treatment of adult cases.

CONTRA-INDICATIONS:
Rifafour e-275 tablets are contra-indicated in:
• patients with hypersensitivity to rifamycins, isoniazid, pyrazinamide, ethambutol or other chemically related medication.
• the presence of jaundice or active hepatic disease.
• patients with optic neuritis.
Safety in pregnancy has not been established.
All agents of Rifafour e-275 tablets are excre[t]ed in breast milk. Safety during lactation has not beer established. Rifafour e-275 should not be used in children under 13 years of age.

WARNINGS:

Liver function should be checked before and during treatment and special care should be exercised in alcoholic patients, the elderly or those with pre-existing liver disease.
Caution should be observed with the use of Rifafour e-275 tablets in the following patients:

- Impaired kidney function: dosage adjustment may be required according to the serum concentration of ethambutol
- Patients with visual defects: should visual disturbances occur during treatment these must be reported immediately and the medicine discontinued pending visual evaluation
- Patients at risk of neuropathy or pyridoxine deficiency, including those who are diabetic, alcoholic, malnourished, uraemic or pregnant: pyridoxine supplementation (in a 10 mg to 50 mg daily dose) is usually required in these instances
- Patients with a history of gout
- Patients with porphyria
- Patients with epilepsy, as convulsions may be precipitated
- Patients with a history of psychosis
- Patients with diabetes: pyrazinamide may cause interference with urine ketone determinations
- Rifampicin may decrease the effect of oral contraceptives and patients are advised to change to non-hormonal methods of birth control
- Treatment with Rifafour e-275 tablets may produce reddish colouration of urine, tears and saliva. Contact lenses may be irreversibly stained.

DOSAGE AND DIRECTIONS FOR USE:
Take Rifafour e-275 tablets with a full glass of water 1 hour before, or 2 hours after a meal. However, if gastrointestinal irritation occurs, the tablets may be taken with food. If aluminium-containing antacids are taken, administer one hour after the tablet dose.
The recommended treatment dosages, based on the patient's body weight, given daily for the 2 month initial-phase treatment in adults and children over 13 years of age are as follows:

30-37 kg	2 tablets
38-54 kg	3 tablets
55 - 70 kg	4 tablets
71 kg and over	5 tablets

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:
Side-effects associated with rifampicin:
Some patients may experience a cutaneous syndrome which presents 2 to 3 hours after a daily or intermittent dose i.e. facial flushing, itching, rash, eye irritation.
A 12 hour "flu" syndrome, usually occurring after 3 to 6 months of intermittent treatment and usually with doses of 20 mg/kg or more, may present as fever, chills, bone pain and malaise.
Gastrointestinal effects include nausea, vomiting, anorexia, diarrhoea and epigastric distress, which may be alleviated by administration with food.
There have been reports of pseudomembranous colitis.
Hepatitis and the prodromal symptoms of hepatitis may occur (nausea, vomiting, unusual tiredness/fatigue).
Rifampicin can cause thrombocytopenia and purpura usually with intermittent regimens. Other haematological adverse effects include eosinophilia, leucopenia and haemolytic anaemia.
Nervous system effects include headache, drowsiness, dizziness, ataxia, numbness, visual disturbances and muscular weakness.
Alterations in kidney function and renal failure have occurred.
Rifampicin may cause orange-red discoloration of urine and other body fluids.
Menstrual disturbances have been reported.
Side-effects associated with isoniazid:
Elevated liver enzymes associated with clinical signs of hepatitis such as nausea, vomiting or fatigue may indicate hepatic damage. The incidence of liver damage is highest in patients over 35 years of age, those who are slow acetylators and those who consume alcohol on a daily basis. Gastrointestinal effects (nausea, vomiting, pellagra) and hypersensitivity reactions (skin eruptions including erythema multiforme, fever, lymphadenopathy, vasculitis) may occur.
Haematological effects have been reported (sideroblastic anaemia, agranulocytosis, haemolytic anaemia, thrombocytopenia, neutropenia, eosinophiliaand less frequently, aplastic anaemia).
Neurological effects include psychotic reactions and convulsions.

Other effects: hyperglycaemia, metabolic acidosis, lupus-like syndrome, rheumatoid syndrome, urinary retention and gynaecomastia. Optic neuritis has also been reported.
Peripheral neuropathy has also been associated with isoniazid administration. Pyridoxine supplementation prevents the development of peripheral neuritis, as well as most other nervous system dysfunctions.

Side-effects associated with pyrazinamide:

The most serious side-effect is hepatotoxicity and its frequency appears to be dose-related. Hyperuricaemia commonly occurs, occasionally accompanied by arthralgia and may lead to attacks of gout. Photosensitivity and skin rash have been reported less frequently. Other side-effects that have been reported are anorexia, nausea and vomiting, malaise, fever, sideroblastic anaemia and dysuria.

Side-effects associated with ethambutol:

Retrobulbar neuritis with a reduction in visual acuity, constriction of visual field, central or peripheral scotoma, and green-red colour blindness may occur, affecting one or both eyes. The degree of visual impairment appears to depend on the dose and duration of therapy. Retinal haemorrhage has occurred less frequently. Renal clearance of urate may be reduced and acute gout has been precipitated. Hypersensitivity reactions include skin rash, pruritis, leucopenia, fever and joint pains. Gastrointestinal disturbances include metallic taste, nausea, vomiting, anorexia and abdominal pain. Other adverse effects: Confusion, disorientation, hallucinations, headache, dizziness, malaise, jaundice or transient liver dysfunction, peripheral neuritis.

SPECIAL PRECAUTIONS:

In the following cases, treatment with Rifafour e-275 tablets should be stopped immediately and the patient evaluated: jaundice, rash and fever, elevated liver enzymes associated with the clinical signs of hepatitis, visual impairment. If liver damage is confirmed, the medicine should not be recommenced.
Treatment should be discontinued permanently should thrombocytopenia, purpura, shock or renal failure occur. Periodic eye examinations during treatment is suggested.

INTERACTIONS:

Rifampicin:
Concurrent use of alcohol, acetaminophen, isoniazid and other hepatotoxic medication may increase the incidence of rifampicin-induced hepatotoxicity. The effectiveness of oestrogen-containing oral preparations is reduced. Rifampicin accelerates the metabolism of certain medicines by inducing microsomal enzymes. Medicines that are affected include: atorvaquone, azathioprine, chloramphenicol, cimetidine, clofibrate, corticosteroids, coumarin anticoagulants, cyclosporin, dapsone, diazepam and other benzodiazepines, doxycycline, azole antifungals (ketoconazole, itraconazole, fluconazole), haloperidol, hexobarbitone, methadone, oral hypoglycaemic agents, phenytoin, quinine, sulphasalazine, thyroxine, theophylline, zidovudine, beta-blockers, digitoxin, digoxin, antiarrhythmic agents (e.g. disopyramide, verapamil) and calcium channel blockers.
Isoniazid:
Chronic use of isoniazid may decrease the plasma clearance and prolong the duration of action of alfentanil, coumarin anticoagulants, benzodiazepines, carbamazepine, phenytoin, ethosuximide, chlorzoxazone, and theophylline. Appropriate adjustment of the anticonvulsant dose may be required. Concurrent use of paracetamol, alcohol, rifampicin and other hepatotoxic medication, may increase the potential for isoniazid-induced hepatotoxicity.
Aluminium-containing antacids may delay absorption and decrease serum concentrations of isoniazid. Ingestion of certain types of cheese e.g. Swiss or Cheshire, or fish e.g. tuna, may result in itching of the skin, rapid or pounding heart, chills or headache.
Glucocorticoid corticosteroids may increase hepatic metabolism and/or excretion of isoniazid.
Concurrent use of cycloserine, disulfiram and other neurotoxic medicines may increase the potential for CNS toxicity. Isoniazid may increase the formation of potentially nephrotoxic inorganic fluoride metabolites when used concurrently with enflurane. Interactions with ketoconazole and miconazole have been reported. False positive reactions with copper sulphate urine glucose tests may occur.
Pyrazinamide:
Pyrazinamide may decrease the efficacy of gout therapy (e.g. allopurinol, colchicine, probenecid or sulphinpyrazone) and dosage adjustments of this medication may be necessary.
Ethambutol:
Concurrent administration of neurotoxic medication with ethambutol may potentiate neurotoxic effects such as optic and peripheral neuritis.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

For symptoms of overdosage, refer to "Side-Effects".
Treatment of overdosage consists of gastric lavage, symptomatic and supportive therapy.

IDENTIFICATION:

Purple, round, film coated tablets.

PRESENTATION:
Securitainers of 40, 60, 80, 100 and 500 tablets.

STORAGE INSTRUCTIONS:
Store in a cool place, below 25°C in well-closed containers, protected from light.
KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER:
34/20.2.3/0187

NAME AND BUSINESS ADDRESS OF THE APPLICANT:
Aventis Pharma (Pty) Ltd
2 Bond Street, Midrand, 1685

DATE OF PUBLICATION OF THIS PACKAGE INSERT:
11 February 2002

Aventis Pharma (Pty) Ltd
2 Bond Street
Midrand
1685

RO2-A0003
Britepak

New addition to this site: April 2005
Source: Hospital Pharmacy

SAEPI HOME PAGE TRADE NAME INDEX GENERIC NAME INDEX FEEDBACK

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19.2 Appendix 2. Package Insert Dolutegravir

TIVICAY- dolutegravir sodium tablet, film coated ViiV Healthcare Company

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIVICAY safely and effectively. See full prescribing information for TIVICAY.

TIVICAY (dolutegravir tablets), for oral use Initial U.S. Approval: 2013

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2017
Dosage and Administration, Pregnancy Testing before Initiation of TIVICAY (2.1)	09/2018
Dosage and Administration, Adults (2.2)	11/2017
Warnings and Precautions, He patotoxicity (5.2)	11/2017
Warnings and Precautions, Fat Redistribution (previous 5.3)	Removed 11/2017
Warnings and Precautions, Embryo-Fetal Toxicity (5.3)	09/2018
Warnings and Precautions, Risk of Adverse Reactions or Loss of Virologic Response (5.4)	11/2017

INDICATIONS AND USAGE

TIVICAY is a human immunodeficiency virus type 1 (HIV-1) integrase strand transfer inhibitor (INSTI) indicated in combination with:

- other antiretroviral agents for the treatment of HIV-1 infection in adults and in pediatric patients weighing at least 30 kg. (1)
- rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent. (1)

DOSAGE AND ADMINISTRATION

- Pregnancy Testing: Perform pregnancy testing before initiation of TIVICAY in adolescents and adults of childbearing potential. (2.1, 5.3)
- May be taken without regard to food. (2.2, 2.3)

Adult Population	**Recommended Dose**

Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirinea (2.2)	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers (2.2, 7.3)	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistanceb (12.4)	50 mg twice daily

a Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.
b Alternative combinations that do not include metabolic inducers should be considered where possible.

Pediatric Patients: (Treatment-naïve or treatment-experienced INSTI-naïve patients weighing at least 30 kg). (2.3)

- If at least 40 kg: The recommended dose is TIVICAY 50 mg once daily.
- Patients 30 kg to less than 40 kg: The recommended dose is TIVICAY 35 mg once daily.
- If certain UGT1A or CYP3A inducers are coadministered, then adjust the weight-based dose of TIVICAY to twice daily. (2.3, 7.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 10 mg, 25 mg, and 50 mg (3)

CONTRAINDICATIONS

Previous hypersensitivity reaction to dolutegravir. (4)

- Coadministration with dofetilide. (4)

WARNINGS AND PRECAUTIONS

- Hype rsensitivity reactions characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury, have been reported. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop, as a delay in stopping treatment may result in a life-threatening reaction. (5.1)
- He patotoxicity has been reported in patients receiving dolutegravir-containing regimens. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations. Monitoring for hepatotoxicity is recommended. (5.2)
- Embryo-fetal toxicity may occur when used at the time of conception and in early pregnancy. Avoid use of TIVICAY at the time of conception through the first trimester of pregnancy due to the risk of neural tube defects. Advise adolescents and adults of childbearing potential to use effective contraception. (2.1, 5.3, 8.1, 8.3)

- Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy. (5.5)

ADVERSE REACTIONS

The most common adverse reactions of moderate to severe intensity and incidence at least 2% (in those receiving TIVICAY in any one adult trial) are insomnia, fatigue, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ViiV Healthcare at 1-877-844 -8872 or FDA at 1-800 -FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Refer to the full prescribing information for important drug interactions with TIVICAY. (4, 7)
- Drugs that are metabolic inducers may decrease the plasma concentrations of dolutegravir. (7.2, 7.3)
- TIVICAY should be taken 2 hours before or 6 hours after taking cation-containing antacids or laxatives, sucralfate, oral supplements containing iron or calcium, or buffered medications. Alternatively, TIVICAY and supplements containing calcium or iron can be taken together with food. (7.3)

USE IN SPECIFIC POPULATIONS

- Pregnancy: Avoid use of TIVICAY at the time of conception through the first trimester due to the risk of neural tube defects. (2.1, 5.3, 8.1)
- Lactation: Breastfeeding is not recommended due to the potential for HIV-1 transmission. (8.2)
- Females and males of reproductive potential: Pregnancy testing and contraception are recommended in adolescents and adults of childbearing potential. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.
Revised: 9 /2018

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TIVICAY is indicated in combination with:

- other antiretroviral agents for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and in pediatric patients weighing at least 30 kg *[see Microbiology (12.4)]*.
- rilpivirine as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen for at least 6 months with no history of treatment failure or known substitutions associated with resistance to either antiretroviral agent.

2 DOSAGE AND ADMINISTRATION

2.1 Pregnancy Testing before Initiation of TIVICAY

Perform pregnancy testing before initiation of TIVICAY in adolescents and adults of childbearing potential *[see Warnings and Precautions (5.3), Use in Specific Populations (8.1, 8.3)]*.

2.2 Adults

TIVICAY tablets may be taken with or without food.

Table 1. Dosing Recommendations for TIVICAY in Adult Patients

Population	Recommended Dose
Treatment-naïve or treatment-experienced INSTI-naïve or virologically suppressed (HIV-1 RNA <50 copies per mL) adults switching to dolutegravir plus rilpivirinea	50 mg once daily
Treatment-naïve or treatment-experienced INSTI-naïve when coadministered with certain UGT1A or CYP3A inducers *[see Drug Interactions (7.3)]*	50 mg twice daily
INSTI-experienced with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistanceb *[see Microbiology (12.4)]*	50 mg twice daily

a Rilpivirine dose is 25 mg once daily for those switching to dolutegravir plus rilpivirine.

b Alternative combinations that do not include metabolic inducers should be considered where possible *[see Drug Interactions (7)]*.

2.3 Pediatric Patients

TIVICAY tablets may be taken with or without food. Treatment-Naïve or Treatment-Experienced INSTI-Naïve
The recommended dose of TIVICAY in pediatric patients weighing at least 30 kg is provided in Table 2.

Table 2. Dosing Recommendations for TIVICAY in Pediatric Patients Weighing at Least 30 kg

Body Weight (kg)	**Daily Dose**a **(Number of Tablets per Dose when Different Strength(s) are Required)**
30 to less than 40	35 mg once daily (One 25-mg tablet and one 10-mg tablet)
40 or greater	50 mg once daily

a If certain UGT1A or CYP3A inducers are coadministered, then increase the weight-based dose of TIVICAY to twice daily *[see Drug Interactions (7.3) for relevant inducers]*.

Safety and efficacy of TIVICAY have not been established in pediatric patients who are INSTI- experienced with documented or clinically suspected resistance to other INSTIs (raltegravir, elvitegravir).

3 DOSAGE FORMS AND STRENGTHS

Tablets:
10 mg: Each tablet contains 10 mg of dolutegravir (as dolutegravir sodium). Tablets are white, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “10” on the other side.
25 mg: Each tablet contains 25 mg of dolutegravir (as dolutegravir sodium). Tablets are pale yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “25” on the other side.
50 mg: Each tablet contains 50 mg of dolutegravir (as dolutegravir sodium). Tablets are yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “50” on the other side.

4 CONTRAINDICATIONS

TIVICAY is contraindicated in patients:

- with previous hypersensitivity reaction to dolutegravir *[see Warnings and Precautions (5.1)]*.
- receiving dofetilide due to the potential for increased dofetilide plasma concentrations and the risk for serious and/or life-threatening events *[see Drug Interactions (7)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions have been reported and were characterized by rash, constitutional findings, and sometimes organ dysfunction, including liver injury. The events were reported in less than 1% of subjects receiving TIVICAY in Phase 3 clinical trials. Discontinue TIVICAY and other suspect agents immediately if signs or symptoms of hypersensitivity reactions develop (including, but not limited to, severe rash or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters or peeling of the skin, oral blisters or lesions, conjunctivitis, facial edema, hepatitis, eosinophilia, angioedema, difficulty breathing). Clinical status, including liver aminotransferases, should be monitored and appropriate therapy initiated. Delay in stopping treatment with TIVICAY or other suspect agents after the onset of hypersensitivity may result in a life-threatening reaction. TIVICAY is contraindicated in patients who have experienced a previous hypersensitivity reaction to dolutegravir.

5.2 Hepatotoxicity

Hepatic adverse events have been reported in patients receiving a dolutegravir-containing regimen. Patients with underlying hepatitis B or C may be at increased risk for worsening or development of transaminase elevations with use of TIVICAY *[see Adverse Reactions (6.1)].* In some cases, the elevations in transaminases were consistent with immune reconstitution syndrome or hepatitis B reactivation particularly in the setting where anti-hepatitis therapy was withdrawn. Cases of hepatic toxicity, including elevated serum liver biochemistries, hepatitis, and acute liver failure have been reported in patients receiving a dolutegravir-containing regimen without pre-existing hepatic disease or other identifiable risk factors. Drug-induced liver injury leading to liver transplant has been reported with TRIUMEQ (abacavir, dolutegravir, and lamivudine). Monitoring for hepatotoxicity is recommended.

5.3 Embryo-Fetal Toxicity

Preliminary data from an observational study showed that TIVICAY was associated with increased risk of neural tube defects when administered at the time of conception and in early pregnancy. As there is limited understanding of reported types of neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of TIVICAY at the time of conception through the first trimester of pregnancy *[see Use in Specific Populations (8.1)].*

If there are plans to become pregnant or if pregnancy is confirmed within the first trimester while on TIVICAY, if possible, switch to an alternative regimen.

Perform pregnancy testing before initiation of TIVICAY in adolescents and adults of childbearing potential to exclude use of TIVICAY during the first trimester of pregnancy *[see Dosage and Administration (2.1)].*

Advise adolescents and adults of childbearing potential to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*

5.4 Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of TIVICAY and other drugs may result in known or potentially significant drug interactions, some of which may lead to *[see Contraindications (4), Drug Interactions (7.3)]:*

- Loss of therapeutic effect of TIVICAY and possible development of resistance.
- Possible clinically significant adverse reactions from greater exposures of concomitant drugs.

For concomitant drugs for which the interaction can be mitigated, please see Table 6 for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during therapy with TIVICAY; review concomitant medications during therapy with TIVICAY; and monitor for the adverse reactions associated with the concomitant drugs.

5.5 Immune Reconstitution Syndrome

Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including TIVICAY. During the initial phase of combination antiretroviral treatment, patients whose immune systems respond may develop an inflammatory response to indolent or residual opportunistic infections (such as *Mycobacterium avium* infection, cytomegalovirus, *Pneumocystis jirovecii* pneumonia [PCP], or tuberculosis), which may necessitate further evaluation and treatment.

Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution; however, the time to onset is more variable and can occur many months after initiation of treatment.

6 ADVERSE REACTIONS

The following serious adverse drug reactions are discussed in other sections of the labeling:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)]*.
- Hepatotoxicity *[see Warnings and Precautions (5.3)].*
- Immune Reconstitution Syndrome *[see Warnings and Precautions (5.5)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials Experience in Adult Subjects

Treatment-Naïve Subjects: The safety assessment of TIVICAY in HIV□1□infected treatment-naïve subjects is based on the analyses of data from 2 international, multicenter, double-blind trials, SPRING-2 (ING113086) and SINGLE (ING114467) and data from the international, multicenter, open-label FLAMINGO (ING114915) trial.

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual nucleoside reverse transcriptase inhibitor (NRTI) treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir

[TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. Through 96 weeks, the rate of adverse events leading to discontinuation was 2% in both treatment arms.
In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg with fixed-dose abacavir sulfate and lamivudine (EPZICOM) once daily or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA) once daily (study treatment was blinded through Week 96 and open-label from Week 96 through Week 144). Through 144 weeks, the rates of adverse events leading to discontinuation were 4% in subjects receiving TIVICAY 50 mg once daily + EPZICOM and 14% in subjects receiving ATRIPLA once daily.
Treatment-emergent adverse reactions (ARs) of moderate to severe intensity observed in at least 2% of subjects in either treatment arm in SPRING-2 and SINGLE trials are provided in Table 3. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 3. Treatment-Emergent Adverse Reactions of at Least Moderate Intensity (Grades 2 to 4) and at Least 2% Frequency in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		**SINGLE**	
System Organ Class/ Preferred Term	**TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**TIVICAY 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
Psychiatric Insomnia				
Depression	<1%	<1%	3%	3%
Abnormal dreams	<1%	<1%	1%	2%
	<1%	<1%	<1%	2%
Nervous System				
Dizziness Headache	<1%	<1%	<1%	5%
	<1%	<1%	2%	2%
Gastrointestinal				
Nausea Diarrhea	1%	1%	<1%	3%
	<1%	<1%	<1%	2%
Skin and Subcutaneous Tissue				
Rasha				
	0	<1%	<1%	6%
General Disorders				
Fatigue	<1%	<1%	2%	2%
Ear and Labyrinth				
Vertigo	0	<1%	0	2%

a Includes pooled terms: rash, rash generalized, rash macular, rash maculo-papular, rash pruritic, and drug eruption.

In addition, Grade 1 insomnia was reported by 1% and less than 1% of subjects receiving TIVICAY and raltegravir, respectively, in SPRING-2; whereas in SINGLE the rates were 7% and 4% for TIVICAY and ATRIPLA, respectively. These events were not treatment limiting.

In a multicenter, open-label trial (FLAMINGO), 243 subjects received TIVICAY 50 mg once daily versus 242 subjects who received darunavir 800 mg/ritonavir 100 mg once daily, both in combination with investigator-selected NRTI background regimen (either EPZICOM or TRUVADA). There were 484 subjects included in the efficacy and safety analyses. Through 96 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY and 6% in subjects receiving darunavir/ritonavir. The ARs observed in FLAMINGO were generally consistent with those seen in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In an international, multicenter, double-blind trial (ING111762, SAILING), 719 HIV□1□infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to 2 agents, including at least one fully active agent. At 48 weeks, the rates of adverse events leading to discontinuation were 3% in subjects receiving TIVICAY 50 mg once daily + background regimen and 4% in subjects receiving raltegravir 400 mg twice daily + background regimen.

The only treatment-emergent AR of moderate to severe intensity with at least 2% frequency in either treatment group was diarrhea, 2% (6 of 354) in subjects receiving TIVICAY 50 mg once daily + background regimen and 1% (5 of 361) in subjects receiving raltegravir 400 mg twice daily + background regimen.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: In a multicenter, open- label, single-arm trial (ING112574, VIKING-3), 183 HIV□1□infected, antiretroviral treatment- experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days and with optimized background therapy from Day 8. The rate of adverse events leading to discontinuation was 4% of subjects at Week 48.

Treatment-emergent ARs in VIKING-3 were generally similar compared with observations with the 50- mg once-daily dose in adult Phase 3 trials.

Virologically Suppressed Subjects: The ARs observed for TIVICAY plus rilpivirine in the Week 48 analysis of pooled data from 2 identical, international, multicenter, open-label trials (SWORD-1 and SWORD-2) of 513 HIV–1-infected, virologically suppressed subjects switching from their current antiretroviral regimen to dolutegravir plus rilpivirine, were consistent with the AR profiles and severities for the individual components when administered with other antiretroviral agents. There were no ARs (Grades 2 to 4) with an incidence of at least 2% in either treatment arm. The rates of adverse events leading to discontinuation were 4% in subjects receiving TIVICAY plus rilpivirine once daily and less than 1% in subjects who remained on their current antiretroviral regimen.

Less Common Adverse Reactions Observed in Treatment-Naïve and Treatment-Experienced Trials: The following ARs occurred in less than 2% of treatment-naïve or treatment-experienced subjects receiving TIVICAY in a combination regimen in any one trial. These events have been included because of their seriousness and assessment of potential causal relationship.

Gastrointestinal Disorders: Abdominal pain, abdominal discomfort, flatulence, upper abdominal pain, vomiting.

Hepatobiliary Disorders: Hepatitis.

Musculoskeletal Disorders: Myositis.

Psychiatric Disorders: Suicidal ideation, attempt, behavior, or completion. These events were observed primarily in subjects with a pre-existing history of depression or other psychiatric illness.

Renal and Urinary Disorders: Renal impairment.

Skin and Subcutaneous Tissue Disorders: Pruritus.

Laboratory Abnormalities:

Treatment-Naïve Subjects: Selected laboratory abnormalities (Grades 2 to 4) with a worsening grade from baseline and representing the worst-grade toxicity in at least 2% of subjects are presented in Table 4. The mean change from baseline observed for selected lipid values is presented in Table 5.

Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 4. Selected Laboratory Abnormalities (Grades 2 to 4) in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysis) and SINGLE Trials (Week 144 Analysis)

	SPRING-2		**SINGLE**	
Laboratory Parameter Preferred Term	**TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**TIVICAY 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
ALT				
Grade 2 (>2.5-5.0 x ULN)	4%	4%	3%	5%
Grade 3 to 4 (>5.0 x ULN)	2%	2%	1%	<1%
AST				
Grade 2 (>2.5-5.0 x ULN)	5%	3%	3%	4%
Grade 3 to 4 (>5.0 x ULN)	3%	2%	1%	3%
Total Bilirubin				
Grade 2 (1.6-2.5 x ULN)	3%	2%	<1%	<1%
Grade 3 to 4 (>2.5 x ULN)	<1%	<1%	<1%	<1%
Creatine kinase				
Grade 2 (6.0-9.9 x ULN)	2%	5%	5%	3%
Grade 3 to 4 (≥10.0 x ULN)	7%	4%	7%	8%
Hyperglycemia				
Grade 2 (126-250	6%	6%	9%	6%

mg/dL) Grade 3 (>250 mg/dL)	<1%	2%	2%	<1%
Lipase Grade 2 (>1.5-3.0 x ULN) Grade 3 to 4 (>3.0 x ULN)	7% 2%	7% 5%	11% 5%	11% 4%
Total neutrophils Grade 2 (0.75-0.99 x 109) Grade 3 to 4 (<0.75 x 109)	4% 2%	3% 2%	4% 3%	5% 3%

ULN = Upper limit of normal.

Table 5. Mean Change from Baseline in Fasted Lipid Values in Treatment-Naïve Subjects in SPRING-2 (Week 96 Analysisa) and SINGLE Trials (Week 144 Analysisa)

	SPRING-2		**SINGLE**	
Laboratory Parameter Preferred Term	**TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)**	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**TIVICAY 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
Cholesterol (mg/dL)	8.1	10.1	24.0	26.7
HDL cholesterol (mg/dL)	2.0	2.3	5.4	7.2
LDL cholesterol (mg/dL)	5.1	6.1	16.0	14.6
Triglycerides (mg/dL)	6.7	6.6	13.6	31.9

a Subjects on lipid-lowering agents at baseline were excluded from these analyses (19 subjects in each arm in SPRING-2, and in SINGLE: TIVICAY + EPZICOM n = 30 and ATRIPLA n = 27). Ninety-four subjects initiated a lipid-lowering agent post-baseline; their last fasted on-treatment values (prior to starting the agent) were used regardless if they discontinued the agent (SPRING-2: TIVICAY n = 9, raltegravir n = 13; SINGLE: TIVICAY + EPZICOM n = 36 and ATRIPLA: n = 36).

Laboratory abnormalities observed in the FLAMINGO trial were generally consistent with observations in SPRING-2 and SINGLE.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: Laboratory abnormalities observed in SAILING were generally similar compared with observations seen in the treatment-naïve (SPRING-2 and SINGLE) trials.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: The most common treatment-emergent laboratory abnormalities (greater than 5% for Grades 2 to 4 combined) observed in VIKING-3 at Week 48 were elevated ALT (9%), AST (8%), cholesterol (10%), creatine kinase (6%), hyperglycemia (14%), and lipase (10%). Two percent (4 of 183) of subjects had a Grade 3 to 4 treatment-emergent hematology laboratory abnormality, with neutropenia (2% [3 of 183]) being the most frequently reported.

Virologically Suppressed Adults: Laboratory abnormalities observed in SWORD-1 and SWORD-2 were generally similar compared with observations seen in the other Phase 3 trials.

Hepatitis B and/or Hepatitis C Virus Co-infection: In Phase 3 trials, subjects with hepatitis B and/or C virus co-infection were permitted to enroll provided that baseline liver chemistry tests did not exceed 5 times the ULN. Overall, the safety profile in subjects with hepatitis B and/or C virus co-infection was similar to that observed in subjects without hepatitis B or C co-infection, although the rates of AST and ALT abnormalities were higher in the subgroup with hepatitis B and/or C virus co- infection for all treatment groups. Grades 2 to 4 ALT abnormalities in hepatitis B and/or C co-infected compared with HIV mono-infected subjects receiving TIVICAY were observed in 18% vs. 3% with the 50-mg once-daily dose and 13% vs. 8% with the 50-mg twice-daily dose. Liver chemistry elevations consistent with immune reconstitution syndrome were observed in some subjects with hepatitis B and/or C at the start of therapy with TIVICAY, particularly in the setting where anti-hepatitis therapy was withdrawn *[see Warnings and Precautions (5.2)]*.

Changes in Serum Creatinine: Dolutegravir has been shown to increase serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function *[see Clinical Pharmacology (12.2)]*. Increases in serum creatinine occurred within the first 4 weeks of treatment and remained stable through 96 weeks. In treatment-naïve subjects, a mean change from baseline of 0.15 mg per dL (range: -0.32 mg per dL to 0.65 mg per dL) was observed after 96 weeks of treatment. Creatinine increases were comparable by background NRTIs and were similar in treatment-experienced subjects.

Clinical Trials Experience in Pediatric Subjects

IMPAACT P1093 is an ongoing multicenter, open-label, non-comparative trial of approximately 160 HIV□1□infected pediatric subjects aged 4 weeks to less than 18 years, of which 46 treatment- experienced, INSTI-naïve subjects aged 6 to less than 18 years have been enrolled *[see Use in Specific Populations (8.4), Clinical Studies (14.2)].*

The adverse reaction profile was similar to that for adults. Grade 2 ARs reported by more than one subject were decreased neutrophil count (n = 3) and diarrhea (n = 2). There were no Grade 3 or 4 drug- related ARs reported. No ARs led to discontinuation.

The Grade 3 or 4 laboratory abnormalities reported in more than one subject were elevated total bilirubin (n = 3) and decreased neutrophil count (n = 2). The changes in mean serum creatinine were similar to those observed in adults.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during postmarketing use. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hepatobiliary Disorders

Acute liver failure, hepatotoxicity. Investigations

Weight increased. Musculoskeletal Arthralgia, myalgia. Psychiatric

Anxiety

7 DRUG INTERACTIONS

7.1 Effect of Dolutegravir on the Pharmacokinetics of Other Agents

In vitro, dolutegravir inhibited the renal organic cation transporters, OCT2 (IC50 = 1.93 microM) and multidrug and toxin extrusion transporter (MATE) 1 (IC50 = 6.34 microM). In vivo, dolutegravir inhibits tubular secretion of creatinine by inhibiting OCT2 and potentially MATE1. Dolutegravir may increase plasma concentrations of drugs eliminated via OCT2 or MATE1 (dofetilide and metformin, Table 6) *[see Contraindications (4), Drug Interactions (7.3)]*.

In vitro, dolutegravir inhibited the basolateral renal transporters, organic anion transporter (OAT) 1 (IC50 = 2.12 microM) and OAT3 (IC50 = 1.97 microM). However, in vivo, dolutegravir did not alter the plasma concentrations of tenofovir or para-amino hippurate, substrates of OAT1 and OAT3.

In vitro, dolutegravir did not inhibit (IC50 greater than 50 microM) the following: cytochrome P450 (CYP)1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A, uridine diphosphate (UDP)-glucuronosyl transferase 1A1 (UGT1A1), UGT2B7, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, OCT1, multidrug resistance protein (MRP)2, or MRP4. In vitro, dolutegravir did not induce CYP1A2, CYP2B6, or CYP3A4. Based on these data and the results of drug interaction trials, dolutegravir is not expected to affect the pharmacokinetics of drugs that are substrates of these enzymes or transporters.

7.2 Effect of Other Agents on the Pharmacokinetics of Dolutegravir

Dolutegravir is metabolized by UGT1A1 with some contribution from CYP3A. Dolutegravir is also a substrate of UGT1A3, UGT1A9, BCRP, and P-gp in vitro. Drugs that induce those enzymes and transporters may decrease dolutegravir plasma concentration and reduce the therapeutic effect of dolutegravir.

Coadministration of dolutegravir and other drugs that inhibit these enzymes may increase dolutegravir plasma concentration.

Etravirine significantly reduced plasma concentrations of dolutegravir, but the effect of etravirine was mitigated by coadministration of lopinavir/ritonavir or darunavir/ritonavir, and is expected to be mitigated by atazanavir/ritonavir (Table 6) *[see Drug Interactions (7.3), Clinical Pharmacology (12.3)]*.
In vitro, dolutegravir was not a substrate of OATP1B1 or OATP1B3.

7.3 Established and Other Potentially Significant Drug Interactions

Table 6 provides clinical recommendations as a result of drug interactions with TIVICAY. These recommendations are based on either drug interaction trials or predicted interactions due to the expected magnitude of interaction and potential for serious adverse events or loss of efficacy. *[See Dosage and Administration (2), Clinical Pharmacology (12.3).]*

Table 6. Established and Other Potentially Significant Drug Interactions: Alterations in Dose or Regimen May Be Recommended Based on Drug Interaction Trials or Predicted Interactions [see Dosage and Administration (2)]

Concomitant Drug Class: Drug Name	**Effect on Concentration of Dolutegravir and/or Concomitant Drug**	**Clinical Comment**
HIV-1 Antiviral Agents		
Non-nucleoside reverse transcriptase inhibitor: Etravirinea	↓Dolutegravir	Use of TIVICAY with etravirine without coadministration of atazanavir/ritonavir, darunavir/ritonavir, or lopinavir/ritonavir is not recommended.
Non-nucleoside reverse transcriptase inhibitor: Efavirenza	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.b
Non-nucleoside reverse transcriptase inhibitor: Nevirapine	↓Dolutegravir	Avoid coadministration with nevirapine because there are insufficient data to make dosing recommendations.

Protease inhibitors: Fosamprenavir/ritonavira Tipranavir/ritonavira	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternative combinations that do not include metabolic inducers where possible for INSTI-experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.b
Other Agents		
Dofetilide	↑Dofetilide	Coadministration is contraindicated with TIVICAY

		[see Contraindications (4)].
Carbamazepinea	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily in treatment-naïve or treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternative treatment that does not include carbamazepine where possible for INSTI- experienced patients with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance.b
Oxcarbazepine Phenytoin Phenobarbital St. John's wort (*Hypericum perforatum*)	↓Dolutegravir	Avoid coadministration with TIVICAY because there are insufficient data to make dosing recommendations.
Medications containing polyvalent cations (e.g., Mg or Al): Cation-containing antacidsa or laxatives Sucralfate Buffered medications	↓Dolutegravir	Administer TIVICAY 2 hours before or 6 hours after taking medications containing polyvalent cations.
Oral calcium or iron supplements, including multivitamins containing calcium or irona	↓Dolutegravir	Administer TIVICAY 2 hours before or 6 hours after taking supplements containing calcium or iron. Alternatively, TIVICAY and supplements containing calcium or iron can be taken together with food.
Metformin	↑Metformin	With concomitant use, limit the total daily dose of metformin to 1,000 mg either when starting metformin or TIVICAY. When stopping TIVICAY, the metformin dose may require an adjustment. Monitoring of blood glucose when initiating concomitant use and after withdrawal of TIVICAY is recommended.

Rifampina	↓Dolutegravir	Adjust dose of TIVICAY to 50 mg twice daily for treatment-naïve and treatment-experienced, INSTI-naïve adult patients. In pediatric patients, increase the weight-based dose to twice daily (Table 2). Use alternatives to rifampin where possible for INSTI-experienced patients with certain INSTI- associated resistance substitutions or clinically suspected INSTI resistance.b

a *See Clinical Pharmacology (12.3) Table 9 or Table 10 for magnitude of interaction.*

b The lower dolutegravir exposures observed in INSTI-experienced patients (with certain INSTI- associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) upon coadministration with certain inducers may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents.

7.4 Drugs without Clinically Significant Interactions with Dolutegravir

Based on drug interaction trial results, the following drugs can be coadministered with dolutegravir without a dose adjustment: atazanavir/ritonavir, darunavir/ritonavir, daclatasvir, elbasvir/grazoprevir, methadone, midazolam, omeprazole, oral contraceptives containing norgestimate and ethinyl estradiol, prednisone, rifabutin, rilpivirine, sofosbuvir/velpatasvir, and tenofovir *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to TIVICAY during pregnancy. Healthcare providers are encouraged to register patients by calling the Antiretroviral Pregnancy Registry (APR) at 1-800-258-4263.

Risk Summary

Preliminary data from an observational study has identified a possible increased risk of neural tube defects when TIVICAY is administered at the time of conception compared with non-dolutegravir- containing antiretroviral regimens. As defects related to closure of the neural tube occur from conception through the first 6 weeks of gestation, embryos exposed to dolutegravir from the time of conception through the first 6 weeks of gestation are at potential risk. In addition, 2 of the 4 birth defects (encephalocele and iniencephaly), which have been observed with dolutegravir use, although often termed neural tube defects, may occur post-neural tube closure, the time period of which may be later than 6 weeks of gestation, but within the first

trimester. Due to the limited understanding of the types of reported neural tube defects associated with dolutegravir use and because the date of conception may not be determined with precision, avoid use of TIVICAY at the time of conception through the first trimester of pregnancy. No neural tube defects have been reported in infants born to mothers who have started TIVICAY after the first trimester of pregnancy *(see Data)*. If there are plans to become pregnant or if pregnancy is confirmed while on TIVICAY during the first trimester, if possible, switch to an alternative regimen. Advise pregnant adolescents and adults of the potential risk to the embryo exposed to TIVICAY from the time of conception through the first trimester of pregnancy.
There are insufficient human data on the use of TIVICAY during pregnancy to definitively assess a drug-associated risk for birth defects and miscarriage. The background risk for major birth defects for the indicated population is unknown. In the U.S. general population, the estimated background rate for major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
In animal reproduction studies, no evidence of adverse developmental outcomes was observed with dolutegravir at systemic exposures (AUC) less than (rabbits) and approximately 27 times (rats) the exposure in humans at the maximum recommended human dose (MRHD) of TIVICAY *(see Data)*.

Data

Human Data: As of May 2018, in an ongoing birth outcome surveillance study in Botswana, there have been 4 cases of neural tube defects reported out of 426 births (0.94%) to mothers who were exposed to dolutegravir-containing regimens at the time of conception. In comparison, the neural tube defect prevalence rates were 0.12% (14/11,300) in the non-dolutegravir arm and 0.09% (61/66,057) in the HIV-uninfected arm. Four cases reported with dolutegravir included one case each of encephalocele, anencephaly, myelomeningocele, and iniencephaly. No infant born to a woman who started dolutegravir during pregnancy had a neural tube defect (n = 2,812).
Data analyzed to date from other sources including the APR, clinical trials, and postmarketing data are insufficient to address the risk of neural tube defects with dolutegravir.
Animal Data: Dolutegravir was administered orally at up to 1,000 mg per kg daily to pregnant rats and rabbits on gestation Days 6 to 17 and 6 to 18, respectively, and to rats on gestation Day 6 to lactation/post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/post-natal (rats) development were observed at up to the highest dose tested. During organogenesis, systemic exposures (AUC) to dolutegravir in rabbits were less than the exposure in humans at the MRHD and in rats were approximately 27 times the exposure in humans at the MRHD. In the rat pre/post-natal development study, decreased body weight of the developing offspring was observed during lactation at a maternally toxic dose (approximately 27 times human exposure at the MRHD).

8.2 Lactation

Risk Summary

The Centers for Disease Control and Prevention recommends that HIV□1□infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection.

It is not known whether TIVICAY is present in human breast milk, affects human milk production, or has effects on the breastfed infant. When administered to lactating rats, dolutegravir was present in milk *(see Data)*. Because of the potential for (1) HIV□1 transmission (in HIV-negative infants), (2) developing viral resistance (in HIV-positive infants), and (3) adverse reactions in a breastfed infant similar to those seen in adults, instruct mothers not to breastfeed if they are receiving TIVICAY.

Data

Animal Data: Dolutegravir was the primary drug-related component excreted into the milk of lactating rats following a single oral dose of 50 mg per kg on lactation Day 10, with milk concentrations of up to approximately 1.3 times that of maternal plasma concentrations observed 8 hours postdose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Perform pregnancy testing in adolescents and adults of childbearing potential before initiation of TIVICAY.

Contraception

Adolescents and adults of childbearing potential should avoid use of TIVICAY at the time of conception through the first trimester of pregnancy because of the potential risk of neural tube defects *[see Use in Specific Populations (8.1)]*.

Advise adolescents and adults of childbearing potential who are taking TIVICAY to consistently use effective contraception.

8.4 Pediatric Use

The safety, virologic, and immunologic responses in subjects who received TIVICAY were evaluated in 46 treatment-experienced, INSTI-naïve, HIV□1–infected subjects aged 6 to less than 18 years in an open-label, multicenter, dose-finding clinical trial, IMPAACT P1093 *[see Clinical Pharmacology (12.3), Clinical Studies (14.2)]*. Frequency, type, and severity of adverse reactions among the 46 pediatric subjects were comparable to those observed in adults *[see Adverse Reactions (6.2)]*. In 17 subjects weighing at least 30 kg, pharmacokinetic parameters of dolutegravir were comparable to adults receiving 50 mg once daily *[see Clinical Pharmacology (12.3)].*

Safety and efficacy of TIVICAY have not been established in pediatric patients weighing less than 30 kg or in any pediatric patients who are INSTI-experienced.

8.5 Geriatric Use

Clinical trials of TIVICAY did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. In general, caution should be exercised in the administration of TIVICAY in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

No clinically important pharmacokinetic differences between subjects with moderate hepatic impairment and matching healthy subjects were observed. No dosage adjustment is necessary for patients with mild to moderate hepatic impairment (Child-Pugh Score A or B). The effect of severe hepatic impairment (Child-Pugh

Score C) on the pharmacokinetics of dolutegravir has not been studied. Therefore, TIVICAY is not recommended for use in patients with severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Renal Impairment

Dolutegravir plasma concentrations were decreased in subjects with severe renal impairment compared with those in matched healthy controls. However, no dosage adjustment is necessary for treatment-naïve or treatment-experienced and INSTI-naïve patients with mild, moderate, or severe renal impairment or for INSTI-experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance) with mild or moderate renal impairment. Caution is warranted for INSTI- experienced patients (with certain INSTI-associated resistance substitutions or clinically suspected INSTI resistance *[see Microbiology (12.4)]*) with severe renal impairment, as the decrease in dolutegravir concentrations may result in loss of therapeutic effect and development of resistance to TIVICAY or other coadministered antiretroviral agents *[see Clinical Pharmacology (12.3)]*.

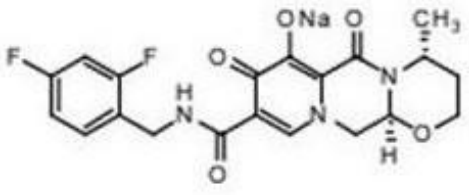
Dolutegravir has not been studied in patients on dialysis.

10 OVERDOSAGE

There is no known specific treatment for overdose with TIVICAY. If overdose occurs, the patient should be monitored and standard supportive treatment applied as required. As dolutegravir is highly bound to plasma proteins, it is unlikely that it will be significantly removed by dialysis.

11 DESCRIPTION

TIVICAY contains dolutegravir, as dolutegravir sodium, an HIV INSTI. The chemical name of dolutegravir sodium is sodium (4*R*,12a*S*)-9-[12]-4-methyl-6,8- dioxo-3,4,6,8,12,12a-hexahydro-2*H*-pyrido[1',2':4,5]pyrazino[2,1-*b*][1,3]oxazin-7-olate. The empirical formula is C20H18F2N3NaO5 and the molecular weight is 441.36 g per mol. It has the following structural formula:



Dolutegravir sodium is a white to light yellow powder and is slightly soluble in water.

Each film-coated tablet of TIVICAY for oral administration contains 10.5, 26.3, or 52.6 mg of dolutegravir sodium, which is equivalent to 10, 25, or 50 mg dolutegravir free acid, respectively, and the following inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium

stearyl fumarate. The tablet film□coating contains the inactive ingredients iron oxide yellow (25-mg and 50-mg tablets only), macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dolutegravir is an HIV-1 antiretroviral agent *[see Microbiology (12.4)].*

12.2 Pharmacodynamics

Effects on Electrocardiogram

In a randomized, placebo-controlled, cross-over trial, 42 healthy subjects received single-dose oral administrations of placebo, dolutegravir 250-mg suspension (exposures approximately 3–fold of the 50-mg once-daily dose at steady state), and moxifloxacin 400 mg (active control) in random sequence. After baseline and placebo adjustment, the maximum mean QTc change based on Fridericia's correction method (QTcF) for dolutegravir was 2.4 msec (1-sided 95% upper CI: 4.9 msec). TIVICAY did not prolong the QTc interval over 24 hours postdose.

Effects on Renal Function

The effect of dolutegravir on renal function was evaluated in an open-label, randomized, 3□arm, parallel, placebo-controlled trial in healthy subjects (n = 37) who received dolutegravir 50 mg once daily (n = 12), dolutegravir 50 mg twice daily (n = 13), or placebo once daily (n = 12) for 14 days. A decrease in creatinine clearance, as determined by 24-hour urine collection, was observed with both doses of dolutegravir after 14 days of treatment in subjects who received 50 mg once daily (9% decrease) and 50 mg twice daily (13% decrease). Neither dose of dolutegravir had a significant effect on the actual glomerular filtration rate (determined by the clearance of probe drug, iohexol) or effective renal plasma flow (determined by the clearance of probe drug, para-amino hippurate) compared with the placebo.

12.3 Pharmacokinetics

The pharmacokinetic properties of dolutegravir have been evaluated in healthy adult subjects and HIV□1–infected adult subjects. Exposure to dolutegravir was generally similar between healthy subjects and HIV□1–infected subjects. The non-linear exposure of dolutegravir following 50 mg twice daily compared with 50 mg once daily in HIV□1–infected subjects (Table 7) was attributed to the use of metabolic inducers in the background antiretroviral regimens of subjects receiving dolutegravir 50 mg twice daily in clinical trials.

Table 7. Dolutegravir Steady-State Pharmacokinetic Parameter Estimates in HIV 1–Infected Adults

Parameter	50 mg Once Daily Geometric Meana (%CV)	50 mg Twice Daily Geometric Meanb (%CV)
AUC(0-24) (mcg.h/mL)	53.6 (27)	75.1 (35)
C_{max} (mcg/mL)	3.67 (20)	4.15 (29)
C_{min} (mcg/mL)	1.11 (46)	2.12 (47)

a Based on population pharmacokinetic analyses using data from SPRING-1 and SPRING-2.
b Based on population pharmacokinetic analyses using data from VIKING (ING112961) and VIKING-3.

Absorption

Following oral administration of dolutegravir, peak plasma concentrations were observed 2 to 3 hours

Post-dose. With once-daily dosing, pharmacokinetic steady state is achieved within approximately 5 days with average accumulation ratios for AUC, C_{max}, and C24 h ranging from 1.2 to 1.5.
Dolutegravir plasma concentrations increased in a less than dose-proportional manner above 50 mg.
Dolutegravir is a P-gp substrate in vitro. The absolute bioavailability of dolutegravir has not been established.
Effect of Food: TIVICAY may be taken with or without food. Food increased the extent of absorption and slowed the rate of absorption of dolutegravir. Low-, moderate-, and high-fat meals increased dolutegravir AUC(0-∞) by 33%, 41%, and 66%; increased C_{max} by 46%, 52%, and 67%; and prolonged T_{max} to 3, 4, and 5 hours from 2 hours under fasted conditions, respectively.

Distribution

Dolutegravir is highly bound (greater than or equal to 98.9%) to human plasma proteins based on in vivo data and binding is independent of plasma concentration of dolutegravir. The apparent volume of distribution (Vd/F) following 50-mg once-daily administration is estimated at 17.4 L based on a population pharmacokinetic analysis.
Cerebrospinal Fluid (CSF): In 12 treatment-naïve subjects on dolutegravir 50 mg daily plus abacavir/lamivudine, the median dolutegravir concentration in CSF was 13.2 ng per mL (range: 3.74 ng per mL to 18.3 ng per mL) 2 to 6 hours post-dose after 16 weeks of treatment. The clinical relevance of this finding has not been established.

Elimination

Dolutegravir has a terminal half-life of approximately 14 hours and an apparent clearance (CL/F) of 1.0 L per hour based on population pharmacokinetic analyses.
Metabolism: Dolutegravir is primarily metabolized via UGT1A1 with some contribution from CYP3A.
Polymorphisms in Drug□Metabolizing Enzymes: In a meta-analysis of healthy subject trials, subjects with UGT1A1 (n = 7) genotypes conferring poor dolutegravir metabolism had a 32% lower clearance of dolutegravir and 46% higher AUC compared with subjects with genotypes associated with normal metabolism via UGT1A1 (n = 41).
Excretion: After a single oral dose of [14C] dolutegravir, 53% of the total oral dose was excreted unchanged in feces. Thirty-one percent of the total oral dose was excreted in urine, represented by an ether glucuronide of dolutegravir (18.9% of total dose), a metabolite formed by oxidation at the benzylic carbon (3.0% of total dose), and its hydrolytic N-dealkylation product (3.6% of total dose). Renal elimination of unchanged drug was low (less than 1% of the dose).

Specific Populations

Pediatric Patients: The pharmacokinetics of dolutegravir in HIV□1–infected children (n = 17) weighing at least 30 kg (dosed by weight bands, receiving either 35 mg or 50 mg) were similar to those observed in HIV□1–infected adults who received dolutegravir 50 mg once daily (Table 8) *[see Clinical Studies (14.2)]*.

Table 8. Dolutegravir Steady-State Pharmacokinetic Parameters in Pediatric Subjects

Weight (n)	Dose of TIVICAY	Dolutegravir Pharmacokinetic Parameter Estimates Geometric Mean (%CV)		
		Cmax (mcg/mL)	AUC(0 -24) (mcg.h/mL)	C24 (mcg/mL)
≥40 kg (n = 14)	50 mg once daily	3.89 (43)	50.1 (53)	0.99 (66)
≥30 to <40 kg (n = 3)	35 mg once daily	4.40 (54)	64.6 (64)	1.33 (93)

Geriatric Patients: Population pharmacokinetic analysis indicated age had no clinically relevant effect on the pharmacokinetics of dolutegravir.

Patients with Hepatic Impairment: In a trial comparing 8 subjects with moderate hepatic impairment (Child-Pugh Score B) with 8 matched healthy controls, exposure of dolutegravir from a single 50-mg dose was similar between the 2 groups. The effect of severe hepatic impairment (Child-Pugh Score C) on the pharmacokinetics of dolutegravir has not been studied.

Patients with Renal Impairment: In a trial comparing 8 subjects with severe renal impairment (CrCl less than 30 mL per min) with 8 matched healthy controls, AUC, Cmax, and C24 of dolutegravir were lower by 40%, 23%, and 43%, respectively, compared with those in matched healthy subjects. Population pharmacokinetic analysis using data from SAILING and VIKING-3 trials indicated that mild and moderate renal impairment had no clinically relevant effect on the exposure of dolutegravir.

Dolutegravir has not been studied in patients requiring dialysis.

HBV or HCV Co-infected Patients: Population analyses using pooled pharmacokinetic data from adult trials indicated no clinically relevant effect of HCV co-infection on the pharmacokinetics of dolutegravir. There were limited data on HBV co-infection.

Gender and Race: Population analyses using pooled pharmacokinetic data from adult trials indicated gender and race had no clinically relevant effect on the exposure of dolutegravir.

Drug Interaction Studies

Drug interaction trials were performed with TIVICAY and other drugs likely to be coadministered or commonly used as probes for pharmacokinetic interactions. The effects of dolutegravir on the exposure of coadministered drugs are summarized in Table 9 and the effects of coadministered drugs on the exposure of dolutegravir are summarized in Table 10.

Dosing or regimen recommendations as a result of established and other potentially significant drug- drug interactions with TIVICAY are provided in Table 6*[see Dosage and Administration (2.2), Drug Interactions (7.3)]*.

Table 9. Summary of Effect of Dolutegravir on the Pharmacokinetics of Coadministered Drugs

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Pharmacokinetic Parameters of Coadministered Drug with/without Dolutegravir No Effect = 1.00		
			Cmax	AUC	Cτ or C24
Daclatasvir 60 mg once daily	50 mg once daily	12	1.03 (0.84 to 1.25)	0.98 (0.83 to 1.15)	1.06 (0.88 to 1.29)
Elbasvir 50 mg once daily	50 mg single dose	12	0.97 (0.89, 1.05)	0.98 (0.93, 1.04)	0.98 (0.93, 1.03)
Ethinyl estradiol 0.035 mg	50 mg twice daily	15	0.99 (0.91 to 1.08)	1.03 (0.96 to 1.11)	1.02 (0.93 to 1.11)
Grazoprevir 200 mg once daily	50 mg single dose	12	0.64 (0.44, 0.93)	0.81 (0.67, 0.97)	0.86 (0.79, 0.93)
Metformin 500 mg twice daily	50 mg once daily	15a	1.66 (1.53 to 1.81)	1.79 (1.65 to 1.93)	_
Metformin 500 mg twice daily	50 mg twice daily	15a	2.11 (1.91 to 2.33)	2.45 (2.25 to 2.66)	_
Methadone 16 to 150 mg	50 mg twice daily	11	1.00 (0.94 to 1.06)	0.98 (0.91 to 1.06)	0.99 (0.91 to 1.07)
Midazolam 3 mg	25 mg once daily	10	_	0.95 (0.79 to 1.15)	_
Norelgestromin 0.25 mg	50 mg twice daily	15	0.89 (0.82 to 0.97)	0.98 (0.91 to 1.04)	0.93 (0.85 to 1.03)
Rilpivirine 25 mg once daily	50 mg once daily	16	1.10 (0.99 to 1.22)	1.06 (0.98 to 1.16)	1.21 (1.07 to 1.38)
Sofosbuvir 400 mg once daily Metabolite (GS-331007)	50 mg once daily	24	0.88 (0.80, 0.98) 1.01 (0.93, 1.10)	0.92 (0.85, 0.99) 0.99 (0.97, 1.01)	NA 0.99 (0.97, 1.01)
Tenofovir disoproxil fumarate 300 mg once daily	50 mg once daily	15	1.09 (0.97 to 1.23)	1.12 (1.01 to 1.24)	1.19 (1.04 to 1.35)
Velpatasvir 100 mg once daily	50 mg once daily	24	0.94 (0.86, 1.02)	0.91 (0.84, 0.98)	0.88 (0.82, 0.94)

a The number of subjects represents the maximum number of subjects that were evaluated.

Table 10. Summary of Effect of Coadministered Drugs on the Pharmacokinetics of Dolutegravir

Coadministered Drug(s) and Dose(s)	Dose of TIVICAY	n	Geometric Mean Ratio (90% CI) of Dolutegravir Pharmacokinetic Parameters with/without Coadministered Drugs No Effect = 1.00		
			Cmax	AUC	Cτ or C24
Atazanavir 400 mg once daily	30 mg once daily	12	1.50 (1.40 to 1.59)	1.91 (1.80 to 2.03)	2.80 (2.52 to 3.11)
Atazanavir/ritonavir 300/100 mg once daily	30 mg once daily	12	1.34 (1.25 to 1.42)	1.62 (1.50 to 1.74)	2.21 (1.97 to 2.47)
Darunavir/ritonavir 600/100 mg twice daily	30 mg once daily	15	0.89 (0.83 to 0.97)	0.78 (0.72 to 0.85)	0.62 (0.56 to 0.69)
Efavirenz 600 mg once daily	50 mg once daily	12	0.61 (0.51 to 0.73)	0.43 (0.35 to 0.54)	0.25 (0.18 to 0.34)
Elbasvir/grazoprevir 50/200 mg once daily	50 mg single dose	12	1.22 (1.05, 1.40)	1.16 (1.00, 1.34)	1.14 (0.95, 1.36)
Etravirine 200 mg twice daily	50 mg once daily	16	0.48 (0.43 to 0.54)	0.29 (0.26 to 0.34)	0.12 (0.09 to 0.16)
Etravirine + darunavir/ritonavir 200 mg + 600/100 mg twice daily	50 mg once daily	9	0.88 (0.78 to 1.00)	0.75 (0.69 to 0.81)	0.63 (0.52 to 0.76)
Etravirine + lopinavir/ritonavir 200 mg + 400/100 mg twice daily	50 mg once daily	8	1.07 (1.02 to 1.13)	1.11 (1.02 to 1.20)	1.28 (1.13 to 1.45)
Fosamprenavir/ritonavir 700 mg/100 mg twice daily	50 mg once daily	12	0.76 (0.63 to 0.92)	0.65 (0.54 to 0.78)	0.51 (0.41 to 0.63)
Lopinavir/ritonavir 400/100 mg twice daily	30 mg once daily	15	1.00 (0.94 to 1.07)	0.97 (0.91 to 1.04)	0.94 (0.85 to 1.05)
Rilpivirine	50 mg	16	1.13	1.12	1.22

25 mg once daily	once daily		(1.06 to 1.21)	(1.05 to 1.19)	(1.15 to 1.30)
Tenofovir 300 mg once daily	50 mg once daily	15	0.97 (0.87 to 1.08)	1.01 (0.91 to 1.11)	0.92 (0.82 to 1.04)
Tipranavir/ritonavir 500/200 mg twice daily	50 mg once daily	14	0.54 (0.50 to 0.57)	0.41 (0.38 to 0.44)	0.24 (0.21 to 0.27)
Antacid (MAALOX) simultaneous administration	50 mg single dose	16	0.28 (0.23 to 0.33)	0.26 (0.22 to 0.32)	0.26 (0.21 to 0.31)
Antacid (MAALOX) 2 h after dolutegravir	50 mg single dose	16	0.82 (0.69 to 0.98)	0.74 (0.62 to 0.90)	0.70 (0.58 to 0.85)
Calcium carbonate 1,200 mg simultaneous administration (fasted)	50 mg single dose	12	0.63 (0.50 to 0.81)	0.61 (0.47 to 0.80)	0.61 (0.47 to 0.80)
Calcium carbonate 1,200 mg simultaneous administration (fed)	50 mg single dose	11	1.07 (0.83 to 1.38)	1.09 (0.84 to 1.43)	1.08 (0.81 to 1.42)
Calcium carbonate 1,200 mg 2 h after dolutegravir	50 mg single dose	11	1.00 (0.78 to 1.29)	0.94 (0.72 to 1.23)	0.90 (0.68 to 1.19)
Carbamazepine 300 mg twice daily	50 mg once daily	16c	0.67 (0.61 to 0.73)	0.51 (0.48 to 0.55)	0.27 (0.24 to 0.31)
Daclatasvir 60 mg once daily	50 mg once daily	12	1.29 (1.07 to 1.57)	1.33 (1.11 to 1.59)	1.45 (1.25 to 1.68)
Ferrous fumarate 324 mg simultaneous administration (fasted)	50 mg single dose	11	0.43 (0.35 to 0.52)	0.46 (0.38 to 0.56)	0.44 (0.36 to 0.54)
Ferrous fumarate 324 mg simultaneous administration (fed)	50 mg single dose	11	1.03 (0.84 to 1.26)	0.98 (0.81 to 1.20)	1.00 (0.81 to 1.23)
Ferrous fumarate 324 mg 2 h after dolutegravir	50 mg single dose	10	0.99 (0.81 to 1.21)	0.95 (0.77 to 1.15)	0.92 (0.74 to 1.13)

Multivitamin (One-A-Day) simultaneous administration	50 mg single dose	16	0.65 (0.54 to 0.77)	0.67 (0.55 to 0.81)	0.68 (0.56 to 0.82)
Omeprazole 40 mg once daily	50 mg single dose	12	0.92 (0.75 to 1.11)	0.97 (0.78 to 1.20)	0.95 (0.75 to 1.21)
Prednisone 60 mg once daily with taper	50 mg once daily	12	1.06 (0.99 to 1.14)	1.11 (1.03 to 1.20)	1.17 (1.06 to 1.28)
Rifampina 600 mg once daily	50 mg twice daily	11	0.57 (0.49 to 0.65)	0.46 (0.38 to 0.55)	0.28 (0.23 to 0.34)
Rifampinb 600 mg once daily	50 mg twice daily	11	1.18 (1.03 to 1.37)	1.33 (1.15 to 1.53)	1.22 (1.01 to 1.48)
Rifabutin 300 mg once daily	50 mg once daily	9	1.16 (0.98 to 1.37)	0.95 (0.82 to 1.10)	0.70 (0.57 to 0.87)

a Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg twice daily.

b Comparison is rifampin taken with dolutegravir 50 mg twice daily compared with dolutegravir 50 mg once daily.

c The number of subjects represents the maximum number of subjects that were evaluated.

12.4 Microbiology

Mechanism of Action

Dolutegravir inhibits HIV integrase by binding to the integrase active site and blocking the strand transfer step of retroviral deoxyribonucleic acid (DNA) integration which is essential for the HIV replication cycle. Strand transfer biochemical assays using purified HIV-1 integrase and pre-processed substrate DNA resulted in IC50 values of 2.7 nM and 12.6 nM.

Antiviral Activity in Cell Culture

Dolutegravir exhibited antiviral activity against laboratory strains of wild-type HIV-1 with mean EC50 values of 0.5 nM (0.21 ng per mL) to 2.1 nM (0.85 ng per mL) in peripheral blood mononuclear cells (PBMCs) and MT-4 cells. Dolutegravir exhibited antiviral activity against 13 clinically diverse clade B isolates with a mean EC50 value of 0.52 nM in a viral integrase susceptibility assay using the integrase coding region from clinical isolates. Dolutegravir demonstrated antiviral activity in cell culture against a panel of HIV-1 clinical isolates (3 in each group of M clades A, B, C, D, E, F, and G, and 3 in group

O) with EC50 values ranging from 0.02 nM to 2.14 nM for HIV-1. Dolutegravir EC50 values against 3 HIV-2 clinical isolates in PBMC assays ranged from 0.09 nM to 0.61 nM.

Antiviral Activity in Combination with Other Antiviral Agents

The antiviral activity of dolutegravir was not antagonistic when combined with the INSTI, raltegravir; non-nucleoside reverse transcriptase inhibitors (NNRTIs), efavirenz or nevirapine; the nucleoside reverse transcriptase inhibitors (NRTIs), abacavir or stavudine; the protease inhibitors (PIs), amprenavir or lopinavir; the CCR5 co-receptor antagonist, maraviroc; or the fusion inhibitor, enfuvirtide.

Dolutegravir antiviral activity was not antagonistic when combined with the HBV reverse transcriptase inhibitor, adefovir, or inhibited by the antiviral, ribavirin.

Resistance

Cell Culture: Dolutegravir-resistant viruses were selected in cell culture starting from different wild- type HIV-1 strains and clades. Amino acid substitutions E92Q, G118R, S153F or Y, G193E or R263K emerged in different passages and conferred decreased susceptibility to dolutegravir of up to 4-fold. Passage of mutant viruses containing the Q148R or Q148H substitutions selected for additional substitutions in integrase that conferred decreased susceptibility to dolutegravir (fold-change increase of 13 to 46). The additional integrase substitutions included T97A, E138K, G140S, and M154I. Passage of mutant viruses containing both G140S and Q148H selected for L74M, E92Q, and N155H.

Treatment-Naïve Subjects: No subjects in the dolutegravir 50-mg once-daily treatment arms of treatment-naïve trials SPRING-2 (96 weeks) and SINGLE (144 weeks) had a detectable decrease in susceptibility to dolutegravir or background NRTIs in the resistance analysis subset (n = 12 with HIV-1 RNA greater than 400 copies per mL at failure or last visit and having resistance data). Two virologic failure subjects in SINGLE had treatment-emergent G/D/E193D and G193G/E integrase substitutions at Week 84 and Week 108, respectively, and 1 subject with 275 copies per mL HIV-1 RNA had a treatment- emergent Q157Q/P integrase substitution detected at Week 24. None of these subjects had a corresponding decrease in dolutegravir susceptibility. No treatment-emergent genotypic resistance to the background regimen was observed in the dolutegravir arm in either the SPRING-2 or SINGLE trials. No treatment-emergent primary resistance substitutions were observed in either treatment group in the FLAMINGO trial through Week 96.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects: In the dolutegravir arm of the SAILING trial for treatment-experienced and INSTI-naïve subjects (n = 354), treatment-emergent integrase substitutions were observed in 6 of 28 (21%) subjects who had virologic failure and resistance data. In 5 of the 6 subjects' isolates emergent INSTI substitutions included L74L/M/I, Q95Q/L, V151V/I (n = 1 each), and R263K (n = 2). The change in dolutegravir phenotypic susceptibility for these 5 subject isolates was less than 2-fold. One subject isolate had pre-existing raltegravir resistance substitutions E138A, G140S, and Q148H at baseline and had additional emergent INSTI- resistance substitutions T97A and E138A/T with a corresponding 148-fold reduction in dolutegravir susceptibility at failure. In the comparator raltegravir arm, 21 of 49 (43%) subjects with post-baseline resistance data had evidence of emergent INSTI-resistance substitutions (L74M, E92Q, T97A, E138Q, G140S/A, Y143R/C, Q148H/R, V151I, N155H, E157Q, and G163K/R) and raltegravir phenotypic resistance.

Virologically Suppressed Subjects: SWORD-1 and SWORD-2 are identical trials in virologically suppressed subjects receiving 2 NRTIs plus either an INSTI, an NNRTI, or a PI, that switched to dolutegravir plus rilpivirine (n = 513) or remained on their current antiviral regimen (n = 511). Two subjects in each treatment arm had confirmed virologic failure at any time through Week 48. The 2 subjects in the dolutegravir/rilpivirine arm had detectable resistance substitutions at rebound. One subject had the NNRTI-resistance-associated substitution K101K/E with no decreased susceptibility to rilpivirine (fold-change = 1.2) at Week 36, had no INSTI resistance-associated substitutions or decreased susceptibility to dolutegravir (fold-change less than 2), and had HIV-1 RNA less than
50 copies per mL at the withdrawal visit. The other subject had the dolutegravir resistance-associated substitution G193E at baseline (by exploratory HIV proviral DNA archive sequencing) and at Week 24 (by conventional sequencing) without decreased susceptibility to dolutegravir (fold-change = 1.02) at Week 24. No resistance-associated substitutions were observed for the other 2 subjects in the comparative current antiretroviral regimen arm.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects: VIKING-3 examined the efficacy of dolutegravir 50 mg twice daily plus optimized background therapy in subjects with prior or current virologic failure on an INSTI- (elvitegravir or raltegravir) containing regimen. Use of TIVICAY in INSTI-experienced patients should be guided by the number and type of baseline INSTI substitutions. The efficacy of TIVICAY 50 mg twice daily is reduced in patients with an INSTI- resistance Q148 substitution plus 2 or more additional INSTI-resistance substitutions, including T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R.

Response by Baseline Genotype

Of the 183 subjects with baseline data, 30% harbored virus with a substitution at Q148, and 33% had no primary INSTI-resistance substitutions (T66A/I/K, E92Q/V, Y143R/C/H, Q148H/R/K, and N155H) at baseline, but had historical genotypic evidence of INSTI-resistance substitutions, phenotypic evidence of elvitegravir or raltegravir resistance, or genotypic evidence of INSTI-resistance substitutions at screening.

Response rates by baseline genotype were analyzed in an “as-treated” analysis at Week 48 (n = 175) (Table 11). The response rate at Week 48 to dolutegravir-containing regimens was 47% (24 of 51) when Q148 substitutions were present at baseline; Q148 was always present with additional INSTI- resistance substitutions (see Table 11). In addition, a diminished virologic response of 40% (6 of 15) was observed when the substitution E157Q or K was present at baseline with other INSTI-resistance substitutions but without a Q148H or R substitution.

Table 11. Response by Baseline Integrase Genotype in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

	Week 48 (<50 copies/mL) n = 175

Overall Response	66% (116/175)
No Q148 substitutiona	74% (92/124)
Q148H/R + G140S/A/C without additional INSTI-resistance substitutionb	61% (17/28)
Q148H/R + ≥2 INSTI-resistance substitutionsb,c	29% (6/21)

a Includes INSTI-resistance substitutions Y143R/C/H and N155H.
b INSTI-resistance substitutions included T66A, L74I/M, E138A/K/T, G140S/A/C, Y143R/C/H, E157Q, G163S/E/K/Q, or G193E/R. Two additional subjects had baseline genotypes of Q148Q/R plus L74L/I/M (virologic failure) and Q148R plus E138K (responder).
c The most common pathway with Q148H/R + greater than or equal to 2 INSTI-resistance substitutions had Q148+G140+E138 substitutions (n = 16).

Response by Baseline Phenotype

Response rates by baseline phenotype were analyzed in an as-treated analysis using all subjects with available baseline phenotypes through Week 48 (n = 163) (see Table 12). These baseline phenotypic groups are based on subjects enrolled in VIKING-3 and are not meant to represent definitive clinical susceptibility cut points for dolutegravir. The data are provided to guide clinicians on the likelihood of virologic success based on pretreatment susceptibility to dolutegravir in INSTI-resistant patients.

Table 12. Response by Baseline Dolutegravir Phenotype (Fold-Change from Reference) in Subjects with Prior Experience to an Integrase Strand Transfer Inhibitor in VIKING-3

Baseline Dolutegravir Phenotype (Fold-Change from Reference)	**Response at Week 48 (<50 copies/mL) Subset n = 163**
Overall Response	64% (104/163)
<3-fold change	72% (83/116)
3- <10-fold change	53% (18/34)
≥10-fold change	23% (3/13)

Integrase Strand Transfer Inhibitor Treatment-Emergent Resistance

There were 50 subjects with virologic failure on the dolutegravir twice-daily regimen in VIKING-3 with HIV-1 RNA greater than 400 copies per mL at the failure timepoint, Week 48 or beyond, or the last timepoint on trial. Thirty-nine subjects with virologic failure had resistance data that were used in the Week 48 analysis. In

the Week 48 resistance analysis 85% (33 of 39) of the subjects with virologic failure had treatment-emergent INSTI-resistance substitutions in their isolates. The most common treatment-emergent INSTI-resistance substitution was T97A. Other frequently emergent INSTI- resistance substitutions included L74M, I or V, E138K or A, G140S, Q148H, R or K, M154I, or N155H. Substitutions E92Q, Y143R or C/H, S147G, V151A, and E157E/Q each emerged in 1 to 3 subjects' isolates. At failure, the median dolutegravir fold-change from reference was 61-fold (range:
0.75 to 209) for isolates with emergent INSTI-resistance substitutions (n = 33).
Resistance to one or more background drugs in the dolutegravir twice-daily regimen also emerged in 49% (19 of 39) of subjects in the Week 48 resistance analysis**.**
In VIKING-4 (ING116529), 30 subjects with current virological failure on an INSTI-containing regimen and genotypic evidence of INSTI-resistance substitutions at screening were randomized to receive either dolutegravir 50 mg twice daily or placebo with the current failing regimen for 7 days and then all subjects received open-label dolutegravir plus optimized background regimen from Day 8.
Virologic responses at Week 48 by baseline genotypic and phenotypic INSTI-resistance categories and the INSTI resistance-associated substitutions that emerged on dolutegravir treatment in VIKING-4 were consistent with those seen in VIKING-3.

Cross-Resistance

Site-Directed Integrase Strand Transfer Inhibitor-Resistant Mutant HIV-1 and HIV-2 Strains: The susceptibility of dolutegravir was tested against 60 INSTI-resistant site-directed mutant HIV-1 viruses (28 with single substitutions and 32 with 2 or more substitutions) and 6 INSTI-resistant site-directed mutant HIV-2 viruses. The single INSTI-resistance substitutions T66K, I151L, and S153Y conferred a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.3-fold to 3.6-fold from reference). Combinations of multiple substitutions T66K/L74M, E92Q/N155H, G140C/Q148R, G140S/Q148H, R or K, Q148R/N155H, T97A/G140S/Q148, and substitutions at E138/G140/Q148 showed a greater than 2-fold decrease in dolutegravir susceptibility (range: 2.5-fold to 21-fold from reference). In HIV-2 mutants, combinations of substitutions A153G/N155H/S163G and E92Q/T97A/N155H/S163D conferred 4-fold decreases in dolutegravir susceptibility, and E92Q/N155H and G140S/Q148R showed 8.5-fold and 17-fold decreases in dolutegravir susceptibility, respectively.
Reverse Transcriptase Inhibitor- and Protease Inhibitor-Resistant Strains: Dolutegravir demonstrated equivalent antiviral activity against 2 NNRTI-resistant, 3 NRTI-resistant, and 2 PI-resistant HIV-1 mutant clones compared with the wild-type strain.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two-year carcinogenicity studies in mice and rats were conducted with dolutegravir. Mice were administered doses of up to 500 mg per kg, and rats were administered doses of up to 50 mg per kg. In mice, no significant

increases in the incidence of drug-related neoplasms were observed at the highest doses tested, resulting in dolutegravir AUC exposures approximately 14 times higher than those in humans at the recommended dose of 50 mg twice daily. In rats, no increases in the incidence of drug- related neoplasms were observed at the highest dose tested, resulting in dolutegravir AUC exposures 10 times and 15 times higher in males and females, respectively, than those in humans at the recommended dose of 50 mg twice daily.

Mutagenesis

Dolutegravir was not genotoxic in the bacterial reverse mutation assay, mouse lymphoma assay, or in the in vivo rodent micronucleus assay.

Impairment of Fertility

In a study conducted in rats, there were no effects on mating or fertility with dolutegravir up to 1,000 mg per kg per day. This dose is associated with an exposure that is approximately 24 times higher than the exposure in humans at the recommended dose of 50 mg twice daily.

14 CLINICAL STUDIES

14.1 Description of Clinical Studies

The efficacy and safety of TIVICAY were evaluated in the studies summarized in Table 13.

Table 13. Trials Conducted with TIVICAY in HIV□1□Infected Subjects

Population	Trial	Trial Arms	Timepoint (Week)
Adults: Treatment- naïve	SPRING-2 (ING113086) (NCT01227824)	TIVICAY + 2 NRTIs (n = 403) Raltegravir +3 NRTIs (n = 405)	96
	SINGLE (ING114467) (NCT01263015)	TIVICAY + EPZICOM (n = 414) ATRIPLA (n = 419)	144
	FLAMINGO (ING114915) (NCT01449929)	TIVICAY + NRTI BR (n = 243) Darunavir/ritonavir + NRTI BR (n = 242)	96
Treatment-experienced, INSTI-naïve	SAILING (ING111762) (NCT01231516)	TIVICAY + BR (n = 354) Raltegravir + BR (n = 361)	48

INSTI-experienced	VIKING-3 (ING112574) (NCT01328041)	TIVICAY + OBT (n = 183)	48
Virologically suppressed	SWORD-1 (NCT02429791) SWORD-2 (NCT02422797)	Pooled presentation TIVICAY + Rilpivirine (n = 513) CAR (n = 511)	48
Pediatrics: 6 years and older without INSTI resistance	IMPAACT P1093 (NCT01302847)	TIVICAY + BR (n = 46)	48

BR = Background regimen; CAR = Current antiretroviral regimen; OBT = Optimized background therapy

14.2 Adult Subjects

Treatment-Naïve Subjects

In SPRING-2, 822 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily, both in combination with fixed-dose dual NRTI treatment (either abacavir sulfate and lamivudine [EPZICOM] or emtricitabine/tenofovir [TRUVADA]). There were 808 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 36 years, 13% female, 15% non-white, 11% had hepatitis B and/or C virus co-infection, 2% were CDC Class C (AIDS), 28% had HIV-1 RNA greater than 100,000 copies per mL, 48% had CD4+ cell count less than 350 cells per mm3, and 39% received EPZICOM; these characteristics were similar between treatment groups.

In SINGLE, 833 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily with fixed-dose abacavir sulfate and lamivudine (EPZICOM) or fixed-dose efavirenz/emtricitabine/tenofovir (ATRIPLA). At baseline, the median age of subjects was 35 years, 16% female, 32% non-white, 7% had hepatitis C co-infection (hepatitis B virus co-infection was excluded), 4% were CDC Class C (AIDS), 32% had HIV-1 RNA greater than 100,000 copies per mL, and 53% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups.

Outcomes for SPRING-2 (Week 96 analysis) and SINGLE (Week 144 open-label phase analysis which followed the Week 96 double-blind phase) are provided in Table 14. Side-by-side tabulation is to simplify presentation; direct comparisons across trials should not be made due to differing trial designs.

Table 14. Virologic Outcomes of Randomized Treatment in SPRING-2 at Week 96 and SINGLE at Week 144 (Snapshot Algorithm)

	SPRING-2	**SINGLE**

	Week 96		Week 144	
	TIVICAY 50 mg Once Daily + 2 NRTIs (n = 403)	**Raltegravir 400 mg Twice Daily + 2 NRTIs (n = 405)**	**TIVICAY 50 mg + EPZICOM Once Daily (n = 414)**	**ATRIPLA Once Daily (n = 419)**
HIV-1 RNA <50 copies/mL	82%	78%	71%	63%
Treatment differencea	4.9% (95% CI: -0.6%, 10.3%)d		8.3% (95% CI: 2.0%, 14.6%)e	
Virologic nonresponse	5%	10%	10%	7%
Data in window not <50 copies/mL	1%	3%	4%	<1%
Discontinued for lack of efficacy	2%	3%	3%	3%
Discontinued for other reasons while not suppressed	<1%	3%	3%	4%
Change in ART regimen	<1%	<1%	0	0
No virologic data	12%	12%	18%	30%
Reasons				
Discontinued study/study drug due to adverse event or deathb	2%	2%	4%	14%
Discontinued study/study drug for other reasonsc	8%	9%	12%	13%
Missing data during window but on study	2%	<1%	2%	3%
Proportion (%) of Subjects with HIV-1 RNA <50 copies/mL by Baseline Category				
Plasma viral load (copies/mL)				
≤100,000	84%	83%	73%	64%
>100,000	79%	63%	69%	61%
Gender				
Male	84%	79%	72%	66%

Female	70%	68%	69%	48%
Race				
White	83%	78%	72%	71%
African-American/African Heritage/Other	77%	75%	71%	47%

a Adjusted for pre-specified stratification factors.
b Includes subjects who discontinued due to an adverse event or death at any time point if this resulted in no virologic data on treatment during the analysis window.
c Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation. d The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 86% in the raltegravir group, with a treatment difference of 2.6% and 95% CI of (-1.9%, 7.2%).
e The primary endpoint was assessed at Week 48 and the virologic success rate was 88% in the group receiving TIVICAY and 81% in the ATRIPLA group, with a treatment difference of 7.4% and 95% CI of (2.5%, 12.3%).

SPRING-2: Virologic outcomes were also comparable across baseline characteristics including CD4+ cell count, age, and use of EPZICOM or TRUVADA as NRTI background regimen. The median change in CD4+ cell counts from baseline was 276 cells per mm3 in the group receiving TIVICAY and
264 cells per mm3 for the raltegravir group at 96 weeks.
There was no treatment-emergent resistance to dolutegravir or to the NRTI background.
SINGLE: Treatment differences were maintained across baseline characteristics including baseline viral load, CD4+ cell count, age, gender, and race.
The adjusted mean changes in CD4+ cell counts from baseline were 378 cells per mm3 in the group receiving TIVICAY + EPZICOM and 332 cells per mm3 for the ATRIPLA group at 144 weeks. The adjusted difference between treatment arms and 95% CI was 46.9 cells per mm3 (15.6 cells per mm3,
78.2 cells per mm3) (adjusted for pre-specified stratification factors: baseline HIV-1 RNA, and baseline CD4+ cell count).
There was no treatment-emergent resistance to dolutegravir, abacavir, or lamivudine.
FLAMINGO: In FLAMINGO, 485 subjects were randomized and received at least 1 dose of either TIVICAY 50 mg once daily (n = 243) or darunavir + ritonavir 800 mg/100 mg once daily (n = 242), both in combination with investigator-selected NRTI background regimen (either fixed-dose abacavir and lamivudine [EPZICOM] or fixed-dose emtricitabine/tenofovir disoproxil fumarate [TRUVADA]).
There were 484 subjects included in the efficacy and safety analyses. At baseline, the median age of subjects was 34 years, 15% female, 28% non-white, 10% had hepatitis B and/or C virus co-infection, 3% were CDC Class C (AIDS), 25% had HIV□1 RNA greater than 100,000 copies per mL, and 35% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups. Overall response rates by

Snapshot algorithm through Week 96 were 80% for TIVICAY and 68% for darunavir/ritonavir. The proportion of subjects who were non-responders (HIV-1 RNA
greater than or equal to 50 copies per mL) at Week 96 was 8% and 12% in the arms receiving TIVICAY and darunavir + ritonavir, respectively; no virologic data were available for 12% and 21% for subjects treated with TIVICAY and darunavir + ritonavir, respectively. The adjusted overall response rate difference in proportion and 95% CI was 12.4% (4.7%, 20.2%). No treatment-emergent primary resistance substitutions were observed in either treatment group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Naïve Subjects

In the international, multicenter, double-blind trial (SAILING), 719 HIV□1□infected, antiretroviral treatment-experienced adults were randomized and received either TIVICAY 50 mg once daily or raltegravir 400 mg twice daily with investigator-selected background regimen consisting of up to
2 agents, including at least 1 fully active agent. There were 715 subjects included in the efficacy and safety analyses. At baseline, the median age was 43 years, 32% were female, 50% non-white, 16% had hepatitis B and/or C virus co-infection, 46% were CDC Class C (AIDS), 20% had HIV-1 RNA greater than 100,000 copies per mL, and 72% had CD4+ cell count less than 350 cells per mm3; these characteristics were similar between treatment groups. All subjects had at least 2-class antiretroviral treatment resistance, and 49% of subjects had at least 3-class antiretroviral treatment resistance at baseline. Week 48 outcomes for SAILING are shown in Table 15.

Table 15. Virologic Outcomes of Randomized Treatment in SAILING at 48 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Once Daily + BRa (n = 354)	**Raltegravir 400 mg Twice Daily + BRa (n = 361)**
HIV-1 RNA <50 copies/mL	71%	64%
Adjustedb treatment difference	7.4% (95% CI: 0.7%, 14.2%)	
Virologic nonresponse	20%	28%
No virologic data	9%	9%
Reasons		
Discontinued study/study drug due to adverse event or death	3%	4%
Discontinued study/study drug for other reasonsc	5%	4%
Missing data during window but on study	2%	1%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category		
Plasma viral load (copies/mL)		
≤50,000 copies/mL	75%	71%
>50,000 copies/mL	62%	47%
Background regimen		

No darunavir use	67%	60%
Darunavir use with primary PI substitutions	85%	67%
Darunavir use without primary PI substitutions	69%	70%
Gender		
Male	70%	66%
Female	74%	60%
Race		
White	75%	71%
African-American/African Heritage/Other	67%	57%

a BR = Background regimen. Background regimen was restricted to less than or equal to 2 antiretroviral treatments with at least 1 fully active agent.
b Adjusted for pre-specified stratification factors.
c Other includes reasons such as withdrew consent, loss to follow-up, moved, and protocol deviation.

Treatment differences were maintained across the baseline characteristics including CD4+ cell count and age. The mean changes in CD4+ cell counts from baseline were 162 cells per mm3 in the group receiving TIVICAY and 153 cells per mm3 in the raltegravir group.

Treatment-Experienced, Integrase Strand Transfer Inhibitor-Experienced Subjects

VIKING-3 examined the effect of TIVICAY 50 mg twice daily over 7 days of functional monotherapy, followed by optimized background therapy (OBT) with continued treatment of TIVICAY 50 mg twice daily.

In the multicenter, open-label, single-arm VIKING-3 trial, 183 HIV□1□infected, antiretroviral treatment-experienced adults with virological failure and current or historical evidence of raltegravir and/or elvitegravir resistance received TIVICAY 50 mg twice daily with the current failing background regimen for 7 days, then received TIVICAY with OBT from Day 8. A total of 183 subjects enrolled: 133 subjects with INSTI resistance at screening and 50 subjects with only historical evidence of resistance (and not at screening). At baseline, median age of subjects was 48 years; 23% were female, 29% non-white, and 20% had hepatitis B and/or C virus co-infection. Median baseline CD4+ cell count was 140 cells per mm3, median duration of prior antiretroviral treatment was 13 years, and 56% were CDC Class C. Subjects showed multiple-class antiretroviral treatment resistance at baseline: 79% had greater than or equal to 2 NRTI, 75% greater than or equal to 1 NNRTI, and 71% greater than or equal to 2 PI major substitutions; 62% had non-R5 virus.

Mean reduction from baseline in HIV-1 RNA at Day 8 (primary endpoint) was 1.4 log10 (95% CI: 1.3 log10, 1.5 log10). Response at Week 48 was affected by baseline INSTI substitutions *[see Microbiology (12.4)]*.

After the functional monotherapy phase, subjects had the opportunity to re-optimize their background regimen when possible. Week 48 virologic outcomes for VIKING-3 are shown in Table 16.

Table 16. Virologic Outcomes of Treatment of VIKING-3 at 48 Weeks (Snapshot Algorithm)

	TIVICAY 50 mg Twice Daily + OBT (n = 183)
HIV-1 RNA <50 copies/mL	63%
Virologic nonresponse	32%
No virologic data Reasons Discontinued study/study drug due to adverse event or death	 3%
Proportion (%) with HIV-1 RNA <50 copies/mL by Baseline Category	
Gender Male Female	 63% 64%
Race White African-American/African Heritage/Other	 63% 64%

Subjects harboring virus with Q148 and with additional Q148-associated secondary substitutions also had a reduced response at Week 48 in a stepwise fashion *[see Microbiology (12.4)].*

The median change in CD4+ cell count from baseline was 80 cells per mm3 at Week 48. Virologically Suppressed Subjects

SWORD-1 and SWORD-2 are identical 148-week, Phase 3, randomized, multicenter, parallel-group, non-inferiority trials. A total of 1,024 adult HIV–1-infected subjects who were on a stable suppressive antiretroviral regimen (containing 2 NRTIs plus either an INSTI, an NNRTI, or a PI) for at least 6 months (HIV-1 RNA less than 50 copies per mL), with no history of treatment failure and no known substitutions associated with resistance to dolutegravir or rilpivirine received treatment in the trials.

Subjects were randomized 1:1 to continue their current antiretroviral regimen or be switched to TIVICAY 50 mg plus rilpivirine 25 mg administered once daily. The primary efficacy endpoint for the SWORD trial was the proportion of subjects with plasma HIV-1 RNA less than 50 copies per mL at Week 48. The proportion of subjects with HIV-1 RNA less than 50 copies per mL at Week 48 was 95% for both treatment groups; treatment difference and 95% CI was -0.2% (-3.0%, 2.5%). The proportion of subjects with HIV-1 RNA greater than or equal to 50 copies per mL (virologic failure) at Week 48 was 0.6% and 1.2% for the dolutegravir plus rilpivirine treatment group and the current antiretroviral regimen treatment groups, respectively; treatment difference and 95% CI was -0.6% (- 1.7%, 0.6%). Refer to the Prescribing Information for JULUCA (dolutegravir and rilpivirine) tablet for complete virologic outcome information.

14.3 Pediatric Subjects

IMPAACT P1093 is a Phase 1/2, 48-week, multicenter, open-label trial to evaluate the pharmacokinetic parameters, safety, tolerability, and efficacy of TIVICAY in combination treatment regimens in HIV□1□infected

infants, children, and adolescents. Subjects were stratified by age, enrolling adolescents first (Cohort 1: aged 12 to less than 18 years) and then younger children (Cohort 2A: aged 6 to less than 12 years). All subjects received a weight-based dose of TIVICAY *[see Dosage and Administration (2.2)]*.

These 46 subjects had a mean age of 12 years (range: 6 to 17), were 54% female and 52% black. At baseline, mean plasma HIV-1 RNA was 4.6 log10 copies per mL, median CD4+ cell count was 639 cells per mm3 (range: 9 to 1,700), and median CD4+% was 23% (range: 1% to 44%). Overall, 39% had baseline plasma HIV-1 RNA greater than 50,000 copies per mL and 33% had a CDC HIV clinical classification of category C. Most subjects had previously used at least 1 NNRTI (50%) or 1 PI (70%).

At Week 24, the proportion of subjects with HIV-1 RNA less than 50 copies per mL in Cohort 1 and Cohort 2A was 70% (16/23) and 61% (14/23), respectively. At Week 48, the proportion of subjects from Cohort 1 with HIV-1 RNA less than 50 copies per mL was 61% (14/23). Virologic outcomes were also evaluated based on body weight. Across both cohorts, virologic suppression (HIV-1 RNA less than 50 copies per mL) at Week 24 was achieved in 75% (18/24) of subjects weighing at least

40 kg and 55% (6/11) of subjects in the 30 to less than 40 kg weight-band. At Week 48, 63% (12/19) of the subjects in Cohort 1 weighing at least 40 kg were virologically suppressed.

The median CD4+ cell count increase from baseline to Week 48 was 84 cells per mm3 in Cohort 1. For Cohort 2A, the median CD4+ cell count increase from baseline to Week 24 was 209 cells per mm3.

16 HOW SUPPLIED/STORAGE AND HANDLING

TIVICAY tablets, 10 mg, are white, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “10” on the other side. Bottle of 30 tablets with child-resistant closure and containing a desiccant. NDC 49702-226-13.

Store and dispense the 10-mg tablets in the original package, protect from moisture, and keep the bottle tightly closed. Do not remove desiccant.

TIVICAY tablets, 25 mg, are pale yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “25” on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702- 227-13.

TIVICAY tablets, 50 mg, are yellow, round, film-coated, biconvex tablets debossed with “SV 572” on one side and “50” on the other side. Bottle of 30 tablets with child-resistant closure. NDC 49702-228- 13.

Store at 25°C (77°F); excursions permitted 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information). Drug Interactions

TIVICAY may interact with other drugs; therefore, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including St. John’s wort *[see Contraindications (4), Drug Interactions (7)]*.

Hypersensitivity Reactions

Advise patients to immediately contact their healthcare provider if they develop rash. Instruct patients to immediately stop taking TIVICAY and other suspect agents, and seek medical attention if they develop a rash associated with any of the following symptoms, as it may be a sign of a more serious reaction such as severe hypersensitivity: fever; generally ill feeling; extreme tiredness; muscle or joint aches; blisters or peeling of the skin; oral blisters or lesions; eye inflammation; facial swelling; swelling of the eyes, lips, tongue, or mouth; breathing difficulty; and/or signs and symptoms of liver problems (e.g., yellowing of the skin or whites of the eyes, dark or tea-colored urine, pale-colored stools or bowel movements, nausea, vomiting, loss of appetite, or pain, aching, or sensitivity on the right side below the ribs) *[see Warnings and Precautions (5.1)]*.

Hepatotoxicity

Inform patients that hepatotoxicity has been reported with dolutegravir *[see Warnings and Precautions (5.2)]*. Advise patients that laboratory monitoring for hepatoxicity during therapy with TIVICAY is recommended, especially for patients with liver disease, such as hepatitis B or C.

Embryo-Fetal Toxicity

Advise adolescents and adults of childbearing potential to avoid use of TIVICAY at the time of conception through the first trimester of pregnancy. Advise adolescents and adults of childbearing potential to contact their healthcare provider if they plan to become pregnant, become pregnant, or if pregnancy is suspected during treatment with TIVICAY *[see Warnings and Precaution (5.3)]*.

Advise adolescents and adults of childbearing potential taking TIVICAY to consistently use effective contraception *[see Use in Specific Populations (8.1, 8.3)]*.

Immune Reconstitution Syndrome

Advise patients to inform their healthcare provider immediately of any signs or symptoms of infection as inflammation from previous infection may occur soon after combination antiretroviral therapy, including when TIVICAY is started *[see Warnings and Precautions (5.5)]*.

Pregnancy Registry

Inform patients that there is an antiretroviral pregnancy registry to monitor fetal outcomes in those exposed to TIVICAY during pregnancy *[see Use in Specific Populations (8.1)]*.

Lactation

Instruct mothers with HIV-1 infection not to breastfeed because HIV-1 can be passed to the baby in the breast milk *[see Use in Specific Populations (8.2)]*.

Missed Dosage

Instruct patients that if they miss a dose of TIVICAY, to take it as soon as they remember. Advise patients not to double their next dose or take more than the prescribed dose *[see Dosage and Administration (2)]*.

Storage

Instruct patients to store the TIVICAY 10-mg tablets in the original package, keep the bottle tightly closed, and protect from moisture. Do not remove desiccant *[see How Supplied/Storage and Handling (16)]*.

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Research Triangle Park, NC 27709 by:
GlaxoSmithKline
Research Triangle Park, NC 27709
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PHARMACIST□DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

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PATIENT INFORMATION TIVICAY (TIV-eh-kay)
(dolutegravir tablets)

What is TIVICAY?
TIVICAY is a prescription medicine that is used to treat Human Immunodeficiency Virus-1 (HIV-1) infection together with:

- other antiretroviral medicines in adults and children who weigh at least 66 pounds (30 kg).
- rilpivirine in adults to replace their current anti-HIV-1 medicines when their healthcare provider determines that they meet certain requirements.

HIV-1 is the virus that causes Acquired Immune Deficiency Syndrome (AIDS).
It is not known if TIVICAY is safe and effective in children who weigh less than 66 pounds (30 kg) or in children who have received certain types of medicine for HIV-1 infection.

Do not take TIVICAY if you:

- have ever had an allergic reaction to a medicine that contains dolutegravir.
- take dofetilide.

Before you take TIVICAY, tell your healthcare provider about all of your medical conditions, including if you:

- have ever had an allergic reaction to dolutegravir.
- have or have had liver problems, including hepatitis B or C infection.
- are pregnant or plan to become pregnant. TIVICAY may harm your unborn baby.
    - **You should not take TIVICAY at the time of becoming pregnant or during the firs t 12 weeks of pregnancy.** Your healthcare provider may change your medicine during this time in your pregnancy.
    - If you can become pregnant, your healthcare provider will perform a pregnancy test before you start treatment with TIVICAY.
    - If you can become pregnant, you should consistently use effective birth control (contraception) during treatment with TIVICAY.
    - Tell your healthcare provider right away if you are planning to become pregnant, you become pregnant, or think you may be pregnant during treatment with TIVICAY.

Pregnancy Registry. There is a pregnancy registry for individuals who take antiretroviral medicines, including TIVICAY, during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.

- are breastfeeding or plan to breastfeed. **Do not breastfeed if you take TIVICAY.**
    - You should not breastfeed if you have HIV-1 because of the risk of passing HIV-1 to your baby.
    - It is not known if TIVICAY can pass to your baby in your breast milk. Talk with your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over- the-counter medicines, vitamins, and herbal supplements.
Some medicines interact with TIVICAY. Keep a list of your medicines and show it to your healthcare provider and pharmacist when you get a new medicine.

- You can ask your healthcare provider or pharmacist for a list of medicines that interact with TIVICAY.
- **Do not start taking a new medicine without telling your healthcare provider.** Your healthcare provider can tell you if it is safe to take TIVICAY with other medicines.

How should I take TIVICAY?

- **Take TIVICAY exactly as your healthcare provider tells you to take it.**
- Take TIVICAY with or without food.
- Do not change your dose or stop taking TIVICAY without talking with your healthcare provider.
- If you take antacids, laxatives, or other medicines that contain aluminum, magnesium, or buffered medicines, TIVICAY should be taken at least 2 hours before or 6 hours after you take these medicines.
- If you need to take iron or calcium supplements by mouth during treatment with TIVICAY:
  - If you take TIVICAY with food, you may take these supplements at the same time that you take TIVICAY.
  - If you do not take TIVICAY with food, take TIVICAY at least 2 hours before or 6 hours after you take these supplements.
- Do not miss a dose of TIVICAY.
- If you miss a dose of TIVICAY, take it as soon as you remember. Do not take 2 doses at the same time or take more than your prescribed dose.
- Stay under the care of a healthcare provider during treatment with TIVICAY.
- Do not run out of TIVICAY. The virus in your blood may increase and the virus may become harder to treat. When your supply starts to run low, get more from your healthcare provider or pharmacy.
- If you take too much TIVICAY, call your healthcare provider or go to the nearest hospital emergency room right away.

What are the possible s ide effects of TIVICAY?

- **TIVICAY can cause serious s ide effects including:**
- **Allergic reactions.** Call your healthcare provider right away if you develop a rash with TIVICAY. **Stop taking TIVICAY and get medical help right away if you develop a rash**

with any of the following signs or symptoms:

- fever
- blisters or peeling of the skin
- generally ill feeling
- redness or swelling of the eyes
- tiredness
- swelling of the mouth, face, lips, or tongue
- muscle or joint aches
- problems breathing
- blisters or sores in mouth

- **Liver problems.** People with a history of hepatitis B or C virus may have an increased risk of developing new or worsening changes in certain liver tests during treatment with TIVICAY. Liver problems, including liver failure, have also happened in people without a history of liver disease or other risk factors. Your healthcare provider may do blood tests to check your liver. **Call your healthcare provider right away if you develop any of the following s igns or symptoms of liver problems** :

- your skin or the white part of your eyes turns yellow (jaundice)
- nausea or vomiting
- loss of appetite
- pain, aching, or tenderness on the right side of your stomach area
- dark or "tea-colored" urine
- light-colored stools (bowel movements)

- **Changes in your immune system (Immune Reconstitution Syndrome)** can happen when you start taking HIV-1 medicines. Your immune system may get stronger and begin to fight infections that have been hidden in your body for a long time. Tell your healthcare provider right away if you start having new symptoms after you start taking TIVICAY.
- **The most common s ide effects of TIVICAY include:**

- trouble sleeping
- tiredness
- headache

These are not all the possible side effects of TIVICAY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1□800□FDA□1088.

How should I store TIVICAY?

- Store TIVICAY at room temperature between 68°F to 77°F (20°C to 25°C).
- Store TIVICAY 10-mg tablets in the original bottle. Keep the bottle tightly closed and protected from moisture.
- The bottle of TIVICAY (10-mg tablets) contains a desiccant packet to help keep your medicine dry (protect it from moisture). Do not remove the desiccant packet from the bottle.

Keep TIVICAY and all medicines out of the reach of children.

General information about the safe and effective use of TIVICAY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TIVICAY for a condition for which it was not prescribed. Do not give TIVICAY to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about TIVICAY that is written for health

professionals. For more information, go to www.TIVICAY.com or call 1-877-844-8872.

What are the ingredients in TIVICAY? Active ingredient: dolutegravir.

Inactive ingredients: D-mannitol, microcrystalline cellulose, povidone K29/32, sodium starch glycolate, and sodium stearyl fumarate. The tablet film□coating contains the inactive ingredients iron oxide yellow (for the 25-mg and 50-mg tablets only), macrogol/PEG, polyvinyl alcohol-part hydrolyzed, talc, and titanium dioxide.

Manufactured for: by:

ViiV Healthcare GlaxoSmithKline

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 09/2018

PRINCIPAL DISPLAY PANEL NDC 49702-226-13

Tivicay®

(dolutegravir) Tablets

Rx Only 10 mg

Each film-coated tablet contains dolutegravir sodium equivalent to 10 mg of dolutegravir.

30 Tablets

Store in original package at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP).

Keep bottle tightly closed; protect from moisture. Do not remove desiccant. See prescribing information for dosage information.

Manufactured for: ViiV Healthcare RTP, NC 27709

by: GlaxoSmithKline RTP, NC 27709

Made in Japan Rev. 5/17 10000000146193



PRINCIPAL DISPLAY PANEL NDC 49702-227-13

Tivicay®

(dolutegravir) Tablets

Rx Only 25 mg

Each film-coated tablet contains dolutegravir sodium equivalent to 25 mg of dolutegravir.

30 Tablets

Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (See USP).

See prescribing information for dosage information. Manufactured for:

ViiV Healthcare RTP, NC 27709

by: GlaxoSmithKline

Research Triangle Park, NC 27709 Made in Japan

Rev. 4/17 10000000146194



PRINCIPAL DISPLAY PANEL NDC 49702-228-13

Tivicay®

(dolutegravir) Tablets

50 mg Rx Only

Each film-coated tablet contains dolutegravir sodium equivalent to 50 mg of dolutegravir.

30 Tablets

Store at controlled room temperature of 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) (see USP).

See prescribing information for dosage information. Manufactured for:

ViiV Healthcare RTP, NC 27709

by: GlaxoSmithKline

Research Triangle Park, NC 27709 Made in Japan

Rev. 6/16 A141767



Product Information			

Active Ingredient/Active Moiety			
Product T ype	HUMAN PRESCRIPTION DRUG	**Ite m Code (Source)**	NDC:49 70 2-226
Route of Administration	ORAL		

Inactive Ingredients		
Ingredient Name	**Basis of Strength**	**Strength**
DO LUTEGRAVIR SO DIUM (UNII: 1Q 1V9 V5WYQ) (DOLUTEGRAVIR - UNII:DKO 1W9 H7M1)	DOLUTEGRAVIR	10 mg

Product Characteristics			
Color	WHITE	**Score**	no sco re

Ingredient Name	Strength
MANNITO L (UNII: 3OWL53L36 A)	
MICRO CRYSTALLINE CELLULO SE (UNII: OP1R32D6 1U)	
PO VIDO NE, UNSPECIFIED (UNII: FZ9 8 9 GH9 4E)	
SO DIUM STARCH GLYCO LATE TYPE A CO RN (UNII: AG9 B6 5PV6 B)	
SO DIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
PO LYETHYLENE GLYCO L, UNSPECIFIED (UNII: 3WJQ 0 SDW1A)	
PO LYVINYL ALCO HO L, UNSPECIFIED (UNII: 532B59 J9 9 0)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	

Shape	ROUND	Size	6 mm

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49 70 2-226-13	30 in 1 BOTTLE; Type 0 : No t a Co mbinatio n Pro duct	0 6 /0 9 /20 16	

Marketing Information			
Marke ting Cate gory	Application Numbe r or Monograph Citation	Marke ting Start Date	Marke ting End Date
NDA	NDA20 479 0	0 6 /0 9 /20 16	

1. TIVICAY

dolutegravir sodium tablet, film coated

Product Information			
Product T ype	HUMAN PRESCRIPTION DRUG	Ite m Code (Source)	NDC:49 70 2-227
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	Basis of Strength	Strength
DO LUTEGRAVIR SO DIUM (UNII: 1Q 1V9 V5WYQ) (DOLUTEGRAVIR - UNII:DKO 1W9 H7M1)	DOLUTEGRAVIR	25 mg

Inactive Ingredients	
Ingredient Name	Strength
MANNITO L (UNII: 3OWL53L36 A)	

MICRO CRYSTALLINE CELLULO SE (UNII: OP1R32D6 1U)	
PO VIDO NE, UNSPECIFIED (UNII: FZ9 8 9 GH9 4E)	
SO DIUM STARCH GLYCO LATE TYPE A CO RN (UNII: AG9 B6 5PV6 B)	
SO DIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
FERRIC O XIDE YELLO W (UNII: EX438 O 2MRT)	
PO LYETHYLENE GLYCO L, UNSPECIFIED (UNII: 3WJQ 0 SDW1A)	
PO LYVINYL ALCO HO L, UNSPECIFIED (UNII: 532B59 J9 9 0)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	

Product Characteristics

Color YELLOW **Score** no sco re

Shape ROUND **Siz e** 7mm

Flavor **Imprint Code** SV;572;25

Contains

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49 70 2-227-13	30 in 1 BOTTLE; Type 0 : No t a Co mbinatio n Pro duct	0 6 /0 9 /20 16	

Marketing Information			
Marke ting Cate gory	Application Numbe r or Monograph Citation	Marke ting Start Date	Marke ting End Date
NDA	NDA20 479 0	0 6 /0 9 /20 16	

2. TIVICAY

dolutegravir sodium tablet, film coated

Product Information			
Product T ype	HUMAN PRESCRIPTION DRUG	**Ite m Code (Source)**	NDC:49 70 2-228
Route of Administration	ORAL		

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
DO LUTEGRAVIR SO DIUM (UNII: 1Q 1V9 V5WYQ) (DOLUTEGRAVIR - UNII:DKO 1W9 H7M1)	DOLUTEGRAVIR	50 mg

Inactive Ingredients	
Ingredient Name	**Strength**
MANNITO L (UNII: 3OWL53L36 A)	
MICRO CRYSTALLINE CELLULO SE (UNII: OP1R32D6 1U)	
PO VIDO NE, UNSPECIFIED (UNII: FZ9 8 9 GH9 4E)	
SO DIUM STARCH GLYCO LATE TYPE A CO RN (UNII: AG9 B6 5PV6 B)	

SO DIUM STEARYL FUMARATE (UNII: 7CV7WJK4UI)	
FERRIC O XIDE YELLO W (UNII: EX438 O 2MRT)	
PO LYETHYLENE GLYCO L, UNSPECIFIED (UNII: 3WJQ 0 SDW1A)	
PO LYVINYL ALCO HO L, UNSPECIFIED (UNII: 532B59 J9 9 0)	
TALC (UNII: 7SEV7J4R1U)	
TITANIUM DIO XIDE (UNII: 15FIX9 V2JP)	

Product Characteristics			
Color	YELLOW	**Score**	no sco re
Shape	ROUND	**Siz e**	9 mm
Flavor		**Imprint Code**	SV;572;50
Contains			

Packaging				
#	Item Code	Package Description	Marketing Start Date	Marketing End Dat
1	NDC:49 70 2-228 -13	30 in 1 BOTTLE; Type 0 : No t a Co mbinatio n Pro duct	0 8 /13/20 13	

Marketing Information

Marke ting Cate gory	Application Numbe r or Monograph Citation	Marke ting Start Date	Marke ting End Date
NDA	NDA20 479 0	0 8 /13/20 13	

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